# EXHIBIT 24

CHAPTER 60

# Inhalation of Inorganic Dust (Pneumoconiosis)



At the Fourth International Pneumoconiosis Conference held in Bucharest in 1971, pneumoconiosis was defined as "the accumulation of dust in the lungs and the tissue reactions to its presence."[1] Such reactions generally take one or both of two clinicopathologic forms.

1. *Fibrosis*, which can be focal and nodular (as in silicosis) or diffuse (as in asbestosis). This process is proba-

bly related to a toxic effect of the inhaled substance on pulmonary epithelial and/or inflammatory cells;[2] it often results in radiographic abnormalities and, if extensive enough, may lead to significant functional impairment.

2. *Aggregates of particle-laden macrophages* with minimal or no accompanying fibrosis, a reaction that is typically seen with inert dusts, such as iron, tin, and barium. Although sometimes associated with chronic radiographic abnormalities, this reaction usually results in few, if any, functional or clinical manifestations.

In addition to these two well-defined pathologic manifestations of disease, there is also evidence that inhaled particles in polluted air may have an important effect on the overall health of the general population,[3] by increasing both the mortality and the morbidity from respiratory disease.[4–7]

To establish a causal relationship between an inhaled dust and an adverse biologic effect in a particular individual or occupational group, demonstration of a history of significant dust exposure as well as abnormalities in pulmonary function, chest radiographs, CT images, or lung structure is required. Analysis of the concentration and particle size of the dust in the workers' "breathing zone" can be useful, and the results should be taken into consideration whenever available. Analysis of inorganic material in the lungs themselves, obtained from either tissue specimens or bronchoalveolar lavage (BAL) fluid samples,[8, 9] can also be helpful. Such analysis ranges from simple examination by standard light microscopy to tissue digestion and particle quantification to energy-dispersive x-ray analysis (*see* page 355).[9a] A detailed occupational history is also important, not only in helping to determine a direct relationship between occupation and disease, but also because certain jobs not usually regarded as harmful can become so if carried out in proximity to other, potentially hazardous occupations, such as welding and sandblasting.[10]

Even when all investigations show convincing evidence for the presence of a pneumoconiosis, the precise cause may not be evident. This uncertainty is related, in part, to the fact that individuals in many occupations are exposed to more than one type of dust; an analysis of lung tissue can reflect this multiplicity, and it is sometimes difficult to attribute pathologic changes to one specific substance. For example, shale miners sometimes develop progressive massive fibrosis similar to that seen in coal miners; their lungs have been shown to contain dust composed of a combination of kaolinite, mica, and silica,[11] each of which can itself cause pulmonary disease. Individuals in numerous other occupations, such as locomotive drivers and stokers, plastics manufacturers,[12] dental technicians,[13–15] foundry workers,[16, 17] welders,[18] and miners and millers of many minerals,[19] are also at risk for the development of pneumoconiosis caused by inhalation of more than one dust; in fact, the term *mixed dust pneumoconiosis* is sometimes used to refer to the ensuing disease.[20] Pathologically, such disease is typically localized to the peribronchiolovascular interstitium and is characterized by the accumulation of numerous dust-containing macrophages and a variable amount of fibrous tissue (Fig. 60–1).

Because pneumoconiosis is by definition related to dust exposure, the disease is strongly associated with the workplace, particularly with jobs that lead to the production of abundant airborne particles. Recognition of the relationship between such particles and pulmonary disease has led to the imposition of government regulations to control the amount of respirable dust in the workplace. Although such regulations have had an effect in reducing both the prevalence and the severity of disease, exposure continues to be poorly controlled in many industries,[21, 22] particularly in "developing" countries.[23] Current surveillance systems for pneumoconiosis probably underestimate the prevalence of disease in the latter regions; however, it is likely that their extent will become more evident in the future as a result of dissemination of knowledge and thorough epidemiologic studies.[24]

Although the inorganic dust pneumoconioses are predominantly occupational diseases, there is no question that they can also develop in individuals who live in the vicinity of industrial plants (particularly those handling asbestos or beryllium) but who do not work there. Such "para-occupational" disease can occur in spouses and children of workers who transport hazardous material on clothing from the workplace into the home[25] or in individuals who simply breathe air contaminated by the nearby mine or industry. Therefore, in any patient in whom the presence of a dust-related disease is suspected, an occupational history should also be obtained from family members. In addition, the site of the patient's residence in relation to industrial plants should be considered. It is also important to remember that inhalation of potentially toxic particles can occur in the house unassociated with their occupational use[26, 27] and in an environment in which there are no hazardous industries (e.g., in association with dust storms[27] or soil that has a high content of a specific mineral[28]).

The reaction of the lung to inhaled inorganic dust depends on many factors, each of which is important by itself but all of which must be considered in combination because they are to a certain extent interdependent. These factors include the chemical nature of the dust, the size and shape of dust particles, the concentration of dust particles in the ambient air, the duration of an individual's exposure to the dust, the rate and pattern of breathing as the dust is inhaled, the distribution and clearance of inhaled dust in the lungs, and individual variations in immune and inflammatory response. These factors are discussed in greater detail on page 126.

## INTERNATIONAL CLASSIFICATION OF RADIOGRAPHS OF THE PNEUMOCONIOSES

The chest radiograph is an important tool in detecting the effects of dust particle deposition in the lungs and in measuring disease progression.[29] For it to be useful in epidemiologic studies, however, it is essential that an acceptable classification of extent of involvement be followed and a standard nomenclature be employed. Several such classifications have been developed over the years, all of which have evolved from the first International Labour Office (ILO) classification contained in the "Report of the International Conference on Silicosis," Johannesburg, 1930.[30] The most widely used schema is the ILO 1980 International Classification of Radiographs of the Pneumoconioses.[30a]

The object of this classification is to codify the radiographic changes of the pneumoconioses in a simple, reproducible manner. Although it does not define pathologic enti-

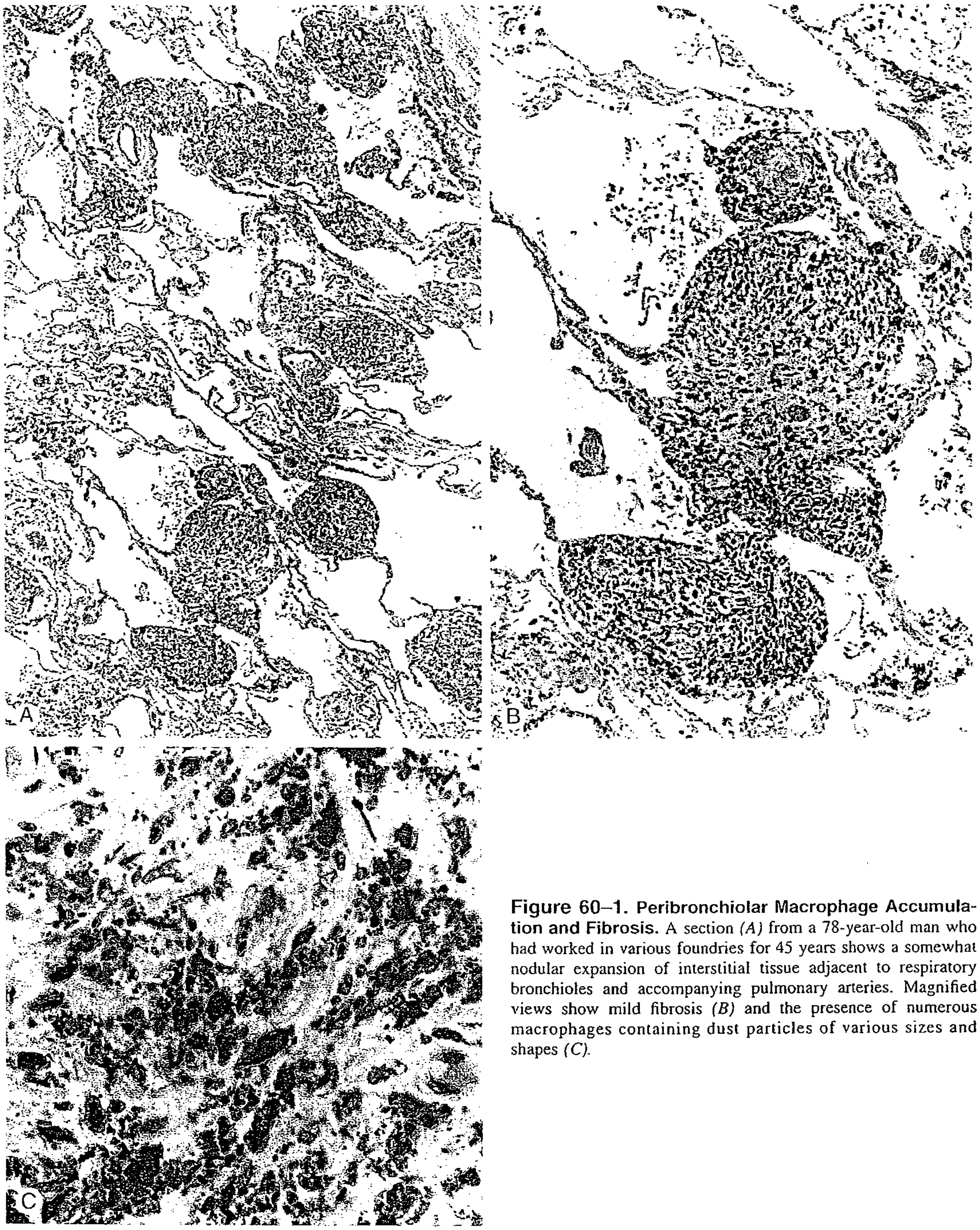



**Figure 60–1. Peribronchiolar Macrophage Accumulation and Fibrosis.** A section *(A)* from a 78-year-old man who had worked in various foundries for 45 years shows a somewhat nodular expansion of interstitial tissue adjacent to respiratory bronchioles and accompanying pulmonary arteries. Magnified views show mild fibrosis *(B)* and the presence of numerous macrophages containing dust particles of various sizes and shapes *(C)*.

ties, it possesses the considerable advantage of providing a uniform, semiquantitative method of reporting the type and extent of disease, thus leading to international comparability of pneumoconiosis statistics. The classification provides a means of systematically recording the radiographic changes in the chest caused by the inhalation of all types of mineral dusts, including coal, silica, carbon, asbestos, and beryllium. It is particularly valuable for epidemiologic studies but is also useful in the evaluation of patients for compensation purposes. Standard reference radiographs have been selected to illustrate the ILO 1980 classification and can be purchased from the ILO office. Because the schema employs radiographic descriptors that are somewhat different from those generally used throughout this book, a short glossary of terms follows.

### International Labour Office Radiographic Terms

Terms requiring explanation are discussed here. All other terms used in the classification are self-explanatory and identical in context to those used elsewhere in this book.

**Small Rounded Opacities.** These are well-circumscribed opacities or nodules ranging in diameter from barely visible up to 10 mm. The qualifiers *p*, *q*, and *r* subdivide the predominant opacities into three diameter ranges—p, up to 1.5 mm; q, 1.5 to 3 mm; and r, 3 to 10 mm.

**Small Irregular Opacities.** This term is employed to describe a pattern that, elsewhere in this book, has been designated *linear*, *reticular*, or *reticulonodular*—in other words, a netlike pattern. Although the nature of these opacities is such that the establishment of quantitative dimensions is considerably more difficult than with rounded opacities, the ILO has seen fit to establish three categories—s, width up to about 1.5 mm; t, width exceeding 1.5 mm and up to about 3 mm; and u, width exceeding 3 mm and up to about 10 mm.

To record shape and size, two letters must be used. Thus, if the reader considers that all or virtually all opacities are one shape and size, this is noted by recording the symbol twice, separated by an oblique stroke (e.g., *q/q*). If another shape or size is seen, this is recorded as the second letter (e.g., *q/t*). The designation *q/t* means that the predominant small opacity is round and of size q but that there are, in addition, a significant number of small irregular opacities of size t. In this way, any combination of small opacities can be recorded.

**Profusion.** This term refers to the number of small rounded or small irregular opacities per unit area or zone of lung. There are four basic categories: category 0, small opacities absent or less profuse than in category 1; category 1, small opacities definitely present but few in number (normal lung markings are usually visible); category 2, numerous small opacities (normal lung markings are usually partly obscured); and category 3, very numerous small opacities (normal lung markings are usually totally obscured). These categories can be further subdivided by employing a 12-point scale, in which there is a continuum of changes from complete normality to the most advanced category or grade:[31, 32]

| | | |
|---|---|---|
| 0/− | 0/0 | 0/1 |
| 1/0 | 1/1 | 1/2 |
| 2/1 | 2/2 | 2/3 |
| 3/2 | 3/3 | 3/+ |

Employing this scale, the radiograph is first classified in the usual way into one of the four categories—0, 1, 2, or 3. If the category above or below is considered as a serious alternative during the process, it is recorded (e.g., a radiograph in which profusion is considered to be category 2 but for which category 1 was seriously considered as an alternative would be graded category 2/1). If no alternative is considered (i.e., the profusion was definitely category 2), it would be classified *2/2*.

A subdivision is also possible within categories 0 and 3. Category 0/1 is profusion of category 0 with category 1 seriously considered as an alternative. Category 0/0 is a radiograph in which there are no small opacities or one in which a few opacities are thought to be present but are not sufficiently definite or numerous for category 1 to be considered. If the absence of small opacities is particularly obvious, profusion should be recorded as 0/−. Such a category might be seen in a healthy nonsmoking adolescent. A radiograph that shows profusion markedly higher than that classifiable as 3/3 would be recorded as 3/+. The ILO standard films are the final arbitrators of opacity profusion and take precedence over any application of a verbal description of profusion. A film is placed in category 1 if it resembles the ILO standard film of the same category and opacity type. Thus, this type of reading should always be done side by side with the ILO standard films.

**Large Opacities.** This term is used for opacities that are larger than the maximum permitted for small rounded opacities (i.e., > 10 mm). Three categories are recognized: category A, an opacity having a greatest diameter exceeding 1 cm up to and including 5 cm or several opacities each greater than 1 cm, the sum of whose greatest diameters does not exceed 5 cm; category B, comprising one or more opacities larger or more numerous than those in category A whose combined area does not exceed the equivalent of the right upper lung zone; and category C, consisting of one or more opacities whose combined area exceeds the equivalent of the right upper lung zone.

**Extent.** Each lung is divided into three zones—upper, middle, and lower—by horizontal lines drawn at one third and two thirds of the vertical distance between the apex of the lung and the dome of the diaphragm.

#### Radiographic Interpretation

Since enactment in 1969 of the U.S. Federal Coal Miners' Health and Safety Act, which provided certain benefits to coal miners who have pneumoconiosis, much attention has been directed toward decision-making processes and observer error in the radiographic diagnosis of pneumoconiosis.[33–35] A common feature of all published reports has been an exceptionally high degree of interreader variability and observer error, which has been attributed to a combination of lack of experience with the classification systems employed, lack of familiarity with the radiographic manifestations of pneumoconiosis, and poor film quality.

As a result of these deficiencies, the National Institute of Occupational Safety and Health (NIOSH) has established an examination that is administered to physicians who wish to be certified as interpreters of chest radiographs in pneumoconiosis programs; the examination is preceded by a weekend course administered by the American College of Radiology. Completion of the course establishes the physician as an *A reader*; successful completion of the examination results in the designation *B reader*. To maintain B reader status, a candidate must undergo a recertification examination every 4 years. Nonexpert readings of films compare poorly with ILO readings when this methodology is used as a screening tool for exposed workers.[36] Expert readers are also unlikely to "overread" films as positive, as illustrated in a large study of nonexposed blue-collar workers.[37] There is little doubt, however, that there is a background level of opacities consistent with the radiographic appearance of pneumoconiosis in populations who do not have occupational exposure to dust.[38, 39] In one meta-analysis in which this issue was addressed, a population prevalence of 5.3% was identified for small densities of profusion greater than or equal to 1/0.[38] The prevalence was significantly greater in Europe (11.3%) than in North America (1.6%), in men (5.5%) than in women (3.5%), and in older than in younger individuals.

In North America, the age-specific pooled prevalence was 2.3% in studies in which the mean patient age was greater than or equal to 50 years and only 0.6% in those in which it was less than 50.

When assessing radiographic progression of simple pneumoconiosis in individual miners, it is recommended that all films be viewed together in known temporal order.[29, 35, 40] Side-by-side reading has been shown to lead to substantially lower observer error and variability than independent reading. The manner of application of the ILO system to epidemiologic studies has been variable,[41] however, making it difficult to compare the findings of all studies in an ideal fashion.

## SILICA

Silica is a ubiquitous, abundant mineral composed of regularly arranged molecules of silicon dioxide ($SiO_2$). It occurs in three forms: (1) *crystalline*, which exists primarily as quartz, tridymite, or cristobalite, depending on the temperature of formation; (2) *microcrystalline*, consisting of minute crystals of quartz bonded together by amorphous silica and exemplified by flint and chert; and (3) *amorphous* (noncrystalline), consisting of kieselguhr (composed of the skeletal remains of diatoms) or vitreous forms (derived by heating and rapid cooling of crystalline material). Occupational exposure to and the fibrogenic potential of these substances vary, a feature that is important in understanding the development of disease in different individuals and different situations. Pure ("free") silica is composed predominantly of $SiO_2$ and must be distinguished from other substances in which $SiO_2$ is combined with an appreciable proportion of cations ("combined" silica, silicates); the latter include asbestos, talc, and mica and are associated with different clinicopathologic forms of disease (*see* farther on).

### Epidemiology

Exposure to a concentration of silica high enough to result in radiographic and pathologic manifestations of silicosis occurs predominantly in occupational settings. Numerous occupations have been associated with such exposure; examples include sandblasting; stonecutting, engraving, and polishing; work with gemstones;[42, 43] the use of clay dye by Japanese rush matting workers;[44] foundry work involving the production of molds, knocking out of castings, and cleaning and polishing (fettling) of the final product;[45] the manufacture of grinding wheels,[46] glass and silica bricks, and crucibles; slate pencil manufacturing;[47, 48] the use of potter's clay and powdered flint in the ceramic industry;[49, 50] and the use of ochre,[51] bentonite,[52] and enamel.[53] The reader is referred to more comprehensive sources for further details of these and other forms of work;[54–59] however, several deserve specific comment.

Because of the ubiquity of silica in the earth's crust, mining, tunneling, and quarrying almost inevitably lead to some exposure to the mineral, unless it involves pure limestone or marble.[57] Thus, the mining of such varied substances as gold, tin, iron, copper, nickel, silver, granite,[51, 60–62] and uranium[57] is a particularly common cause of silicosis. Moreover, the mining of other minerals recognized as causes of pneumoconiosis—such as coal, tungsten,[63] and barium[64, 65]—can also be accompanied by silica exposure, and there is no doubt that the lung disease that appears in some individuals who work with these minerals results from "contaminating" silica, at least in part.

Diatomaceous earth is used in the manufacture of paints, varnishes, and insecticides and in filtration and other processes.[66–69] Although generally considered to be relatively inert in its amorphous form, the substance is converted into cristobalite and tridymite when heated,[57] and exposure to these substances has been associated with a rare but apparently virulent form of disease. Silica flour is a finely ground form of the mineral composed of 99% $SiO_2$; it has been employed as an abrasive, paint extender, and filler for cosmetics and other manufactured items.[70] Its use as an abrasive scouring powder was among the earliest recognized causes of the acute variety of silicosis (*see* farther on);[71, 72] more recently, its use as a polisher or buffer has been reported to be responsible for cases of silicosis in gemstone[73] and jade[74] workers in Hong Kong and in furniture workers in Japan.[75] In one study of 1,809 workers involved in mining and processing of diatomaceous earth in a California facility, evidence of silicosis was identified in 81 (4.5%).[75a]

Although the nature of the occupations involved in exposure to silica dust limits the disease mainly to men, roughly half the individuals at risk in the pottery industry are women, many of whom exhibit typical features of pneumoconiosis.[76] One form of environmental lung disease characterized by increased silica deposition is seen predominantly in women. This variety is associated with the inhalation of fine sand particles and is thus encountered principally in deserts, such as the Negev in Israel.[77] Histologic examination of the lungs of a number of affected individuals has revealed only increased silica deposition without the usual silicotic reaction, leading to the designation *simple siliceous pneumoconiosis* rather than silicosis. This disease is both environmental and occupational because it may involve increased dust inhalation in the tents during the making of cloth from sheep's wool. It is analogous to the Transkei silicosis that is restricted to Bantu women who grind their food with sandstone, thus freeing large amounts of silica particles into the air.[78] Other environmental, nonoccupational exposure to silica causing disease has occurred in some Himalayan populations[79, 80] and in individuals who have perversely inhaled domestic scouring powder.[81–83]

Although the precise incidence and prevalence of silicosis are difficult to assess, there can be little doubt that the disease is one of the most frequent of the pneumoconioses. It has been estimated that as many as 3 million workers in 238,000 processing plants in the United States are potentially exposed to silica dust.[84] Although government regulations in some countries limit the severity of such exposure, current surveillance systems for silicosis likely underestimate the prevalence of the disease because exposure continues to be poorly controlled in many industries.[21, 22, 85–88] In one investigation of 577 people who had silicosis and were reported to the Michigan Department of Public Health between 1987 and 1995, more than half were from hospital identification of disease;[89] most had advanced silicosis, and less than half had applied for compensation. Although most

patients had begun working in iron foundries in the 1930s or 1940s and had been exposed to silica dust for more than 20 years, about 15% had exposure to dust beginning in the 1960s or later, including three whose first exposure was in the 1980s. In the United States, silicosis was listed on death certificates as a primary or contributing cause of death in more than 4,000 workers between 1979 and 1990;[90] some of them have been young adults.[90a]

In "developing" countries, the situation is much worse. For example, in a study of 1,520 black South African gold miners who died from "unnatural" causes in 1990–1991, approximately 13% were found to have evidence of silicosis at autopsy.[91] In China, almost 75,000 cases of silicosis were identified between 1949 and 1986;[92] among the pneumoconioses, it accounted for the greatest potential years of life and work lost.

## Pathogenesis

In addition to clinical and pathologic observations, numerous investigations of experimental animals and cell cultures have resulted in the recognition of a variety of factors that may be important in the pathogenesis of silica-induced pulmonary disease. Such factors must attempt to explain the two fundamental histologic reactions to inhaled silica: (1) the *silicotic nodule*, which is characterized by dense, often concentric lamellae of collagen and which when multiple and conglomerated result in a lesion termed *progressive massive fibrosis* (PMF)*; and (2) *silicoproteinosis*, which typically occurs in individuals or animals exposed to high concentrations of silica and which is characterized by alveolar filling by lipoproteinaceous material similar to that seen in idiopathic alveolar proteinosis. The majority of experimental studies have focused on the first of these reactions because it is by far the more common.[56, 93–96a]

As might be expected, the likelihood of disease and its severity are determined to a large extent by the intensity of exposure to crystalline silica dust. The U.S. Public Health Service statements of concentration of dust particles in the atmosphere describe primary and secondary thresholds. The *primary threshold* consists of $5 \times 10^6$ particles less than 10 μm in size per cubic foot; exposure to concentrations below this level does not result in silicosis. The *secondary threshold* consists of $100 \times 10^6$ particles of the same size per cubic foot; all persons exposed at or above this level acquire silicosis. Although the risk for silicosis is thus related to total exposure, the latent period for its development appears to be largely independent of dose.[97] In addition, because of the typical long latency for the development of silicosis after exposure, because disease may progress after exposure has ceased, and because silicosis may be diagnosed only after the worker has left the workforce, estimates of risk after any given exposure may be flawed.[90] The appreciation of this uncertainty has called into question the appropriateness of certain safety standards and has led to the proposal of the more stringent exposure standard of 0.05 mg/m$^3$ by NIOSH.

The interaction of silica with the pulmonary macrophage is a key factor in the pathogenesis of silicosis. Shortly after deposition of dust in alveolar ducts, pulmonary alveolar macrophages become concentrated in the area,[98] an event possibly initiated by activation of complement present in the alveolar lining fluid.[99] Such activation releases C5a, a powerful macrophage chemoattractant.[100] The inhaled particles are ingested by alveolar macrophages or penetrate to the interstitium, where they may be engulfed by tissue macrophages.[56] There is evidence that the latter react differently to silica than alveolar macrophages[101] and that this reaction is more important in the pathogenesis of ensuing fibrosis.[102, 103]

The fundamental physicochemical characteristic of silica responsible for its toxicity is uncertain. It appears likely to be related to its surface properties, perhaps surface charge,[104] and is unassociated with solubility and surface area.[93] Although early *in vitro* studies suggested that silica ingestion resulted in macrophage death and the release of a variety of toxic products,[105–107] it now appears that alveolar macrophages that have ingested silica have normal viability and basal function *in vivo*.[108, 109] The results of both human[110–112] and animal[113, 114] studies have shown that such silica-exposed macrophages release a variety of fibroblast growth factors, including tumor necrosis factor (TNF),[113] macrophage-derived growth factor,[115] transforming growth factor-β,[112] interferon,[116] fibronectin,[111, 117] and interleukin-1 (IL-1).[118, 119] These substances appear to be associated with the subsequent accumulation of fibroblasts and fibroblast products.[93] Although macrophages may also release products that inhibit fibroblast activation, such as prostaglandin $E_2$,[121] there is evidence that that this is relatively unimportant in the pathogenesis of the disease.[110] An increased amount of IL-10 has been found to be produced by cells in BAL fluid after silica exposure in a murine model of silicosis;[122] although this was associated with an anti-inflammatory effect, the fibrotic response to silica in the lung was unexpectedly amplified in the long term. In humans exposed to inorganic dusts, oxidant release from macrophages is also enhanced;[123, 124] these toxic chemicals may act by causing epithelial cell damage, thereby facilitating the exposure of interstitial cells, such as fibroblasts, to the products of macrophage and lymphocyte secretion.[96]

The interaction of macrophages with other inflammatory or immune cells is also likely to be important in the pathogenesis of silicosis.[120, 125] Lymphocytes—particularly T-helper cells—are increased in number in BAL fluid from both patients and experimental animals that have silicosis.[126, 127] Inflammatory mediators, such as IL-1, induce T lymphocytes to release IL-2,[118, 119] which creates an expanded population of activated helper T lymphocytes. These, in turn, may secrete mediators that activate and amplify macrophage function.[93]

Several observations support the hypothesis that immune-related tissue damage is involved in the pathogenesis of silicosis, including the presence of a variety of serologic abnormalities—such as rheumatoid factor, antinuclear antibodies,[128] immune complexes,[129, 130] and polyclonal gamma globulin[130, 131]—and, occasionally, clinical evidence of immune disturbance,[132–138] particularly kidney disease.[132, 133, 139, 140] Protein adsorbed onto silica crystals can theoretically act as an antigen, and it has been speculated that the silicotic nodule contains antigen-antibody precipitates.[131] BAL fluid

*Although some lesions do not appear to be progressive and, according to the size definition, many are clearly not massive, the term "progressive massive fibrosis" is firmly entrenched in the literature and is used throughout this text.

from patients who have silicosis also contains an increased quantity of immunoglobulin that appears to be produced locally.[141] It is possible that collagen itself serves as the antigen for these reactions,[142-144] resulting in a cycle in which antibodies stimulate macrophages to enhance fibrosis, thereby increasing antibody response in a positive feedback fashion.

Polymorphonuclear leukocytes are an important source of proteolytic enzymes and reactive oxygen species and could theoretically be responsible for some tissue damage in silicosis.[145] These cells have been shown to accumulate in the lungs of silica-exposed individuals, with or without evidence of silicosis.[108] Leukotriene $B_4$ released from macrophages has been implicated as a chemoattractant in the process.[113] There is also experimental evidence that mast cells are involved.[146] Because BAL fluid in patients who have silicosis contains significant amounts of protease and elastase inhibitors,[147] the quantitative effect of neutrophils in the pathogenesis of silicosis is uncertain.[94]

The reasons for the development of PMF in some individuals and not others are unclear. In general, it is associated with a high lung content of silica,[148] a history of tuberculosis,[149, 150] or a background of increased profusion of small opacities.[149] It is possible that genetic differences may explain variations in disease severity among workers who have similar dust exposures; for example, workers who have PMF have a higher prevalence of HLA-AW19,[151] and an excess prevalence of HLA A29 and B44 has been described in workers with simple silicosis.[152] Environmental factors, such as cigarette smoke or inhaled fibrogenic particles in addition to silica, may also be involved. For example, there is evidence that cigarette smoke increases epithelial permeability to silica;[153] because the severity of fibrosis may be related to the amount of silica reaching the interstitial tissue,[102, 103] this may be important in explaining individual reactions.

In contrast to the fibrosis associated with chronic, relatively low-dose exposure to silica, it is perhaps surprising that acute exposure to large amounts of dust results in little collagen deposition in both animals[154] and humans.[155, 156] Instead, it is associated with the production of abundant intra-alveolar proteinaceous material, virtually identical histologically and ultrastructurally to that seen in alveolar proteinosis.[156] The pathogenesis of this reaction is unclear. Experimentally, instillation of silica into the lungs is followed by type I alveolar cell injury and type II cell hyperplasia and hypertrophy,[157, 158] suggesting that an increase in surfactant-producing cells might be a factor. Although it is theoretically possible that silica also directly stimulates type II cells to manufacture and secrete excessive alveolar lining material, experimental findings suggest that this does not occur.[159, 160]

It has also been hypothesized that silica may disturb the ability of macrophages to clear normally produced surfactant from the alveolar air space, thus resulting in its increase at this site.[161] Freshly fractured silica possesses a greater biologic reactivity than the aged form;[162] for example, oxidant production has been found to be enhanced and antioxidant production depressed when silica is freshly fractured rather than aged.[163] Because acute silicoproteinosis is associated with occupations in which fractured silica is likely to be generated, it is possible that these or other related effects are important in the pathogenesis of the disease. The reason for the lack of fibrosis in acute silicoproteinosis is also unclear; however, it has been shown that coating silica particles with alveolar lining material results in significantly less cytotoxicity for ingesting macrophages,[164] a finding that may result in decreased production of fibrogenic mediators relative to classic silicosis. Altered macrophage function probably underlies the greater susceptibility to tuberculosis of patients who have both silicosis and acute silicoproteinosis; *Mycobacterium tuberculosis* grows much more rapidly in cultures of macrophages exposed to sublethal doses of quartz than in those without such exposure.[165]

### Pathologic Characteristics

The pathologic features of silicosis have been reviewed in detail in a report by the Silicosis and Silicate Disease Committee of NIOSH.[166] Grossly, silicotic nodules range from 1 to 10 mm in diameter and typically are more numerous in the upper lobes and parahilar regions than elsewhere (Fig. 60–2). Cut sections show the nodules to be more or less well defined, spherical or irregularly shaped, and firm to hard in texture; calcification or ossification is occasionally present. Depending on the admixture of other dusts, the nodules range in color from slate gray to dense black. Coalescence of nodules results in larger masses that can occupy virtually an entire lobe (PMF) (Fig. 60–3). Such masses are usually associated with adjacent (irregular) emphysema and may be cavitated as a result of ischemia, tuberculosis, or infection by anaerobic organisms.[167] Bronchopulmonary lymph nodes are often somewhat enlarged and rubbery in consistency as a result of fibrosis; the latter may extend beyond the nodal capsule into the adjacent bronchial wall and may be associated with distortion of the underlying bronchial anatomy (Fig. 60–4) and, rarely, significant airway stenosis.[167a]

Microscopically, the earliest lesions are characteristically located in the peribronchiolar, interlobular septal, and pleural interstitial tissues. Initially, they consist predominantly of macrophages with scattered reticulin fibers. As the lesions enlarge, the central portions become hypocellular and composed of mature collagen, sometimes arranged in more or less concentric lamellae; a peripheral zone of macrophages and lesser numbers of plasma cells and lymphocytes surrounds this central portion (Fig. 60–5). Occasionally, the inflammation is granulomatous in nature, similar to that seen in Caplan's lesions of coal workers' pneumoconiosis (CWP) (*see* farther on). Type II cells adjacent to the fibrotic region may be hyperplastic and presumably are the source from which these cells have been identified in BAL specimens.[168] A variable number of birefringent silicate crystals 1 to 3 μm in length can usually be identified by polarization microscopy in the cellular areas of the fibrotic nodules (*see* Fig. 60–5); these can also be identified by their metachromatic staining with toluidine blue.[169] Occasionally, crystals are not apparent with polarization microscopy, and more sophisticated techniques, such as scanning electron microscopy, are required to reveal their presence.[170]

The larger conglomerate lesions of PMF are also composed of hyalinized collagen admixed with variable numbers of pigmented macrophages. The concentric lamellar appearance of the collagen seen in silicotic nodules is frequently

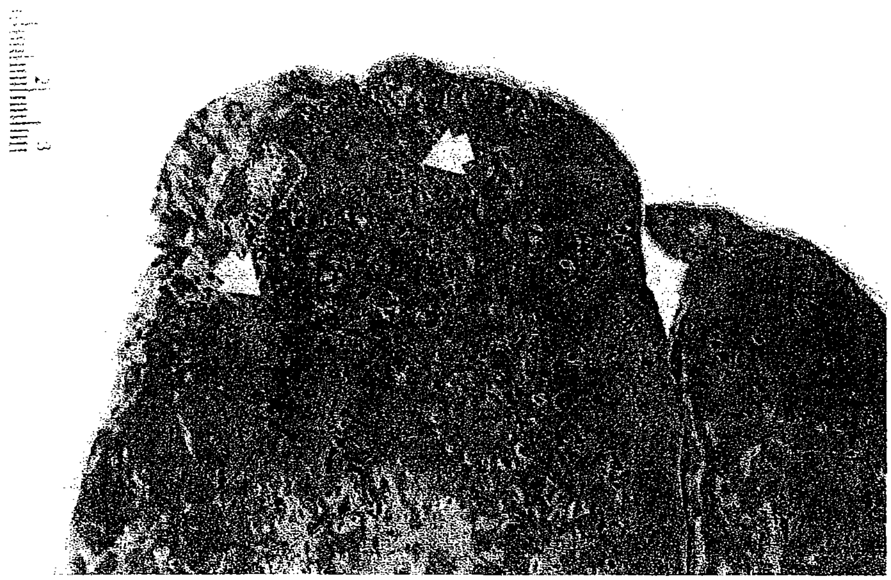


**Figure 60–2. Silicosis: Silicotic Nodules.** A slice of an upper lobe and superior segment of the lower lobe shows multiple well-defined, somewhat irregularly shaped nodules within the lung parenchyma *(arrows)*. The nodules are black as a result of the presence of abundant anthracotic pigment.

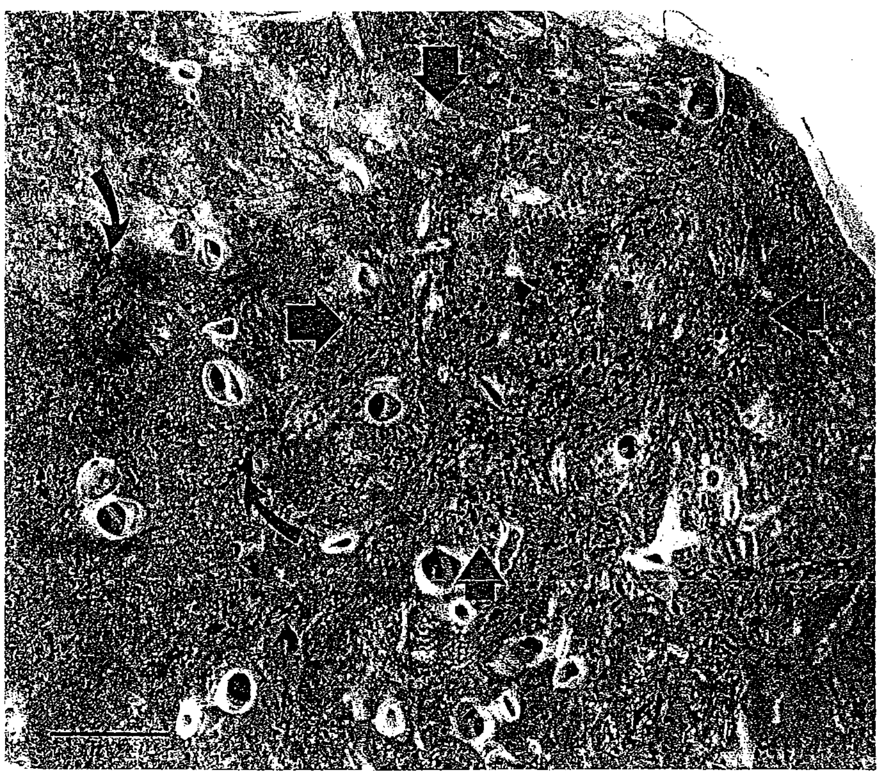


**Figure 60–3. Silicosis: Progressive Massive Fibrosis.** A magnified view of the posterior segment of the right upper lobe shows several small discrete silicotic nodules *(curved arrows)*. In addition, confluence of nodules has resulted in an irregularly shaped area of fibrosis approximately 3 × 4 cm in extent *(indicated by large arrows)*. (Bar = 1 cm.)


**Figure 60–4. Silicosis: Bronchial Wall Fibrosis.** A focus of fibrosis caused by silicosis has extended outside a peribronchial lymph node into the adjacent bronchial wall (the node itself is not visible in the illustration). The fibrous tissue and pigment-laden macrophages extend into the submucosa; the bronchial cartilage plates (C) are somewhat distorted. Note the cholesterol clefts *(arrow)* and focal necrosis (N) indicating the histologic changes of progressive massive fibrosis. (×15.)

not evident. Focal necrosis is common in the central portions (Fig. 60–6) and is occasionally associated with granulomatous inflammation, in which case the presence of tuberculous infection should be considered.

Fibrotic nodules identical to those found in the lungs can also be identified elsewhere in the body (sometimes in individuals with no history of significant occupational dust exposure,[171] in which case their origin is unclear). As might be expected, they are most frequent in the hilar and mediastinal lymph nodes; in fact, in our experience, this is the most common pathologic manifestation of silica exposure, presumably reflecting relatively greater concentration of dust at these sites than in the lungs and decreased exposure of the worker population as a result of government regulations. As in peribronchial lymph nodes, the fibrous reaction may extend outside the nodal capsule into adjacent mediastinal tissue; because of this spread and the firmness of the nodes, there may be confusion with metastatic carcinoma at mediastinoscopy or intraoperative mediastinal exploration. Fibrotic nodules caused by silica are also occasionally found in the liver, spleen, intra-abdominal lymph nodes, and bone marrow.[139, 171a]

The pathologic findings in acute heavy silica exposure differ significantly from those described previously. Although there may be mild interstitial fibrosis and focal small nodular lesions, well-defined collagenous nodules are typically absent. Instead, alveolar air spaces are more or less diffusely filled by somewhat granular, periodic acid–Schiff (PAS)–positive proteinaceous material identical to that seen in idiopathic alveolar proteinosis (Fig. 60–7). Macrophages are present in increased numbers, and alveolar type II cells show a varying degree of hyperplasia and hypertrophy. Ultrastructurally, the intra-alveolar material contains macrophages and desquamated type II cells as well as membranous material resembling that seen in the normal alveolar lining layer.[156]

### Radiologic Manifestations

The classic radiographic pattern of silicosis consists of multiple nodular opacities ranging from 1 to 10 mm in diameter (Figs. 60–8 and 60–9). The nodules are usually well circumscribed and of uniform density. Although profusion can be fairly even throughout both lungs, there is commonly considerable upper lobe predominance. The nodules also tend to involve mainly the posterior portion of the lungs (*see* Fig. 60–8).[172] Nodules have been identified on pathologic examination that were not seen on premortem chest radiographs in many cases.[173] Calcification of nodules is evident on the radiograph in 10% to 20% of cases (Fig. 60–10). A reticular pattern may be seen when silicosis is caused by diatomaceous earth[66, 67] but is distinctly uncommon in other settings.

The radiographic pattern of small round or irregular opacities is commonly referred to as *simple* silicosis, in contrast to *complicated* silicosis (PMF). The latter is characterized by large opacities (conglomerate shadows) (Fig. 60–11) usually in the upper lobes (Fig. 60–12). By definition, the opacities measure greater than 1 cm in diameter; they may become very large (Fig. 60–13), exceeding the volume of an upper lobe in aggregate. The shadow margins may be irregular and somewhat ill-defined or smooth,[174] creating an interface that parallels the lateral chest wall (*see* Fig. 60–13). The opacities commonly develop in the midzone or periphery of the lung; with time, they tend to migrate toward the hilum, leaving emphysematous lung between the fibrotic tissue and the pleural surface.[175] Although usually bilateral, unilateral opacities may occur and may be confused with carcinoma (Fig. 60–14). Cavitation develops occasionally. The more extensive the conglomerate fibrosis, the less apparent is nodularity in the remainder of the lungs (*see* Fig. 60–14).[175] There is seldom any radiographic evidence of pleural abnormality.

*Text continued on page 2402*

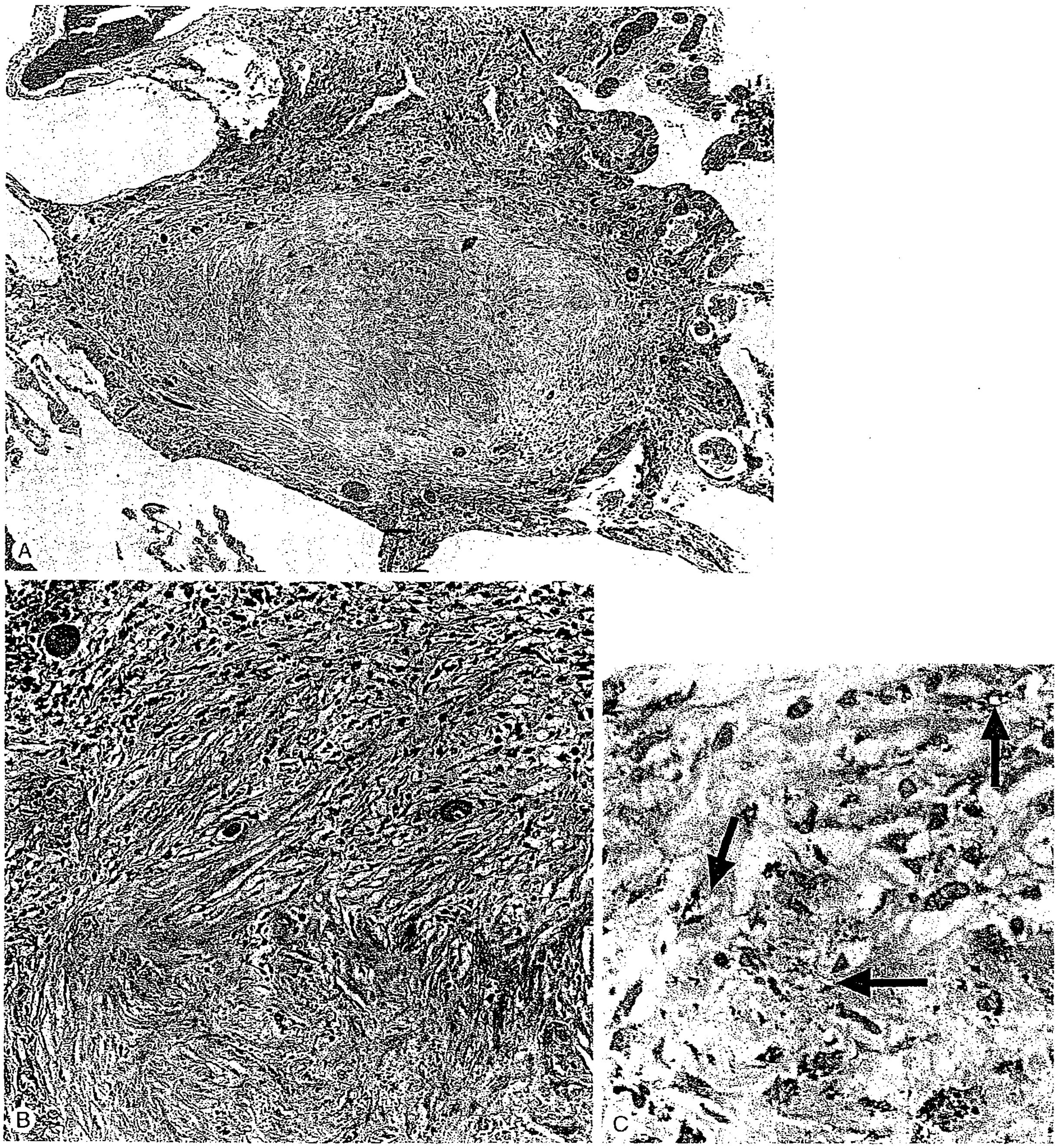



**Figure 60–5. Silicotic Nodule.** A histologic section *(A)* shows a typical silicotic nodule consisting of a central zone of dense collagen and a peripheral rim of macrophages in which abundant foreign particulate material is situated. A section at higher magnification *(B)* shows these characteristics to better advantage. (*A*, ×40; *B*, ×150.) Magnified view *(C)* of macrophages with polarization microscopy shows multiple variably sized and shaped refractile (white) particles *(arrows)* consistent with silicates.

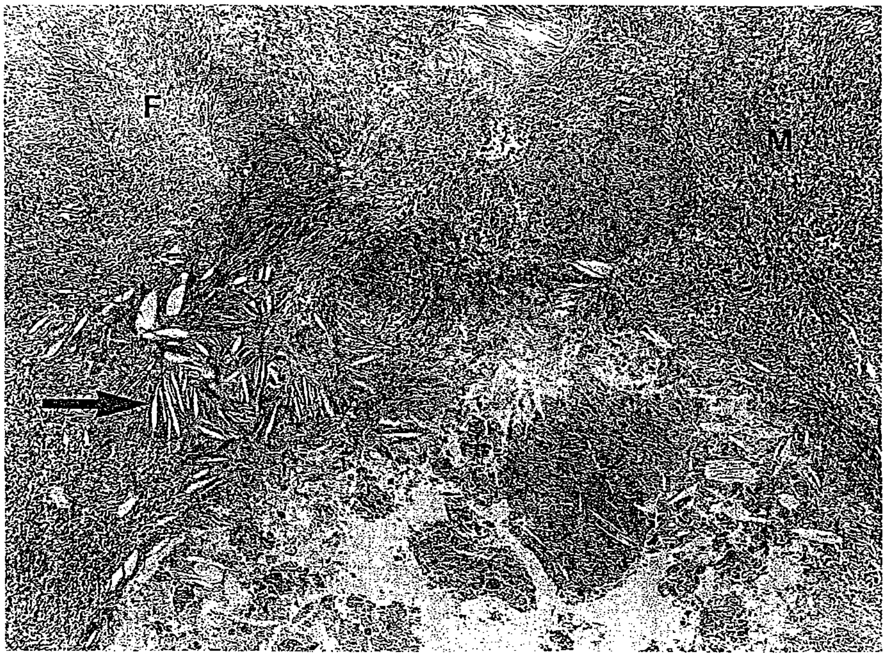



**Figure 60–6. Silicosis: Progressive Massive Fibrosis.** A section from the central portion of the confluent nodular mass illustrated in Figure 60–3 reveals fibrosis (F), aggregates of pigment-laden macrophages (M), and multiple cholesterol clefts *(arrow)*. The tissue in the lower half of the illustration is necrotic and has undergone liquefaction. (×25.)

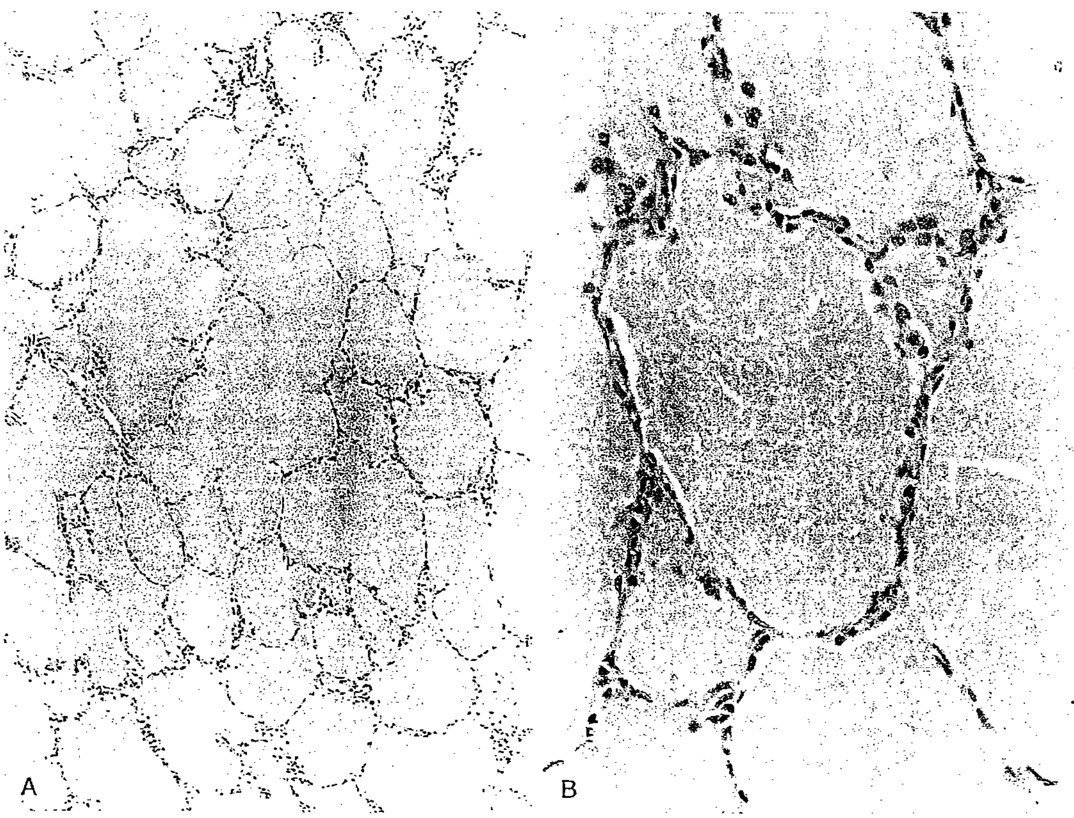



**Figure 60–7. Silicoproteinosis.** Sections show extensive air-space filling by finely granular proteinaceous material identical to that seen in idiopathic alveolar proteinosis. Alveolar septa are essentially unremarkable. The patient was a 25-year-old dental technician who was exposed to a large quantity of silica dust while manufacturing dental prostheses. (Courtesy of Dr. Joachim Majo, Barcelona, Spain.)

**Figure 60–8. Silicosis: Characteristic Radiographic Findings.** A posteroanterior chest radiograph *(A)* demonstrates multiple nodules mainly in the middle and upper lung zones. A lateral radiograph *(B)* reveals that most of the nodules are situated in the posterior half of the lungs. The nodules measure more than 3 mm in diameter (International Labour Office [ILO] r shape). Their profusion is 2/1, slightly less than the ILO standard radiograph for a profusion of 2/2 but considerably more than that with a score of 1/1. The patient was a 60-year-old miner.

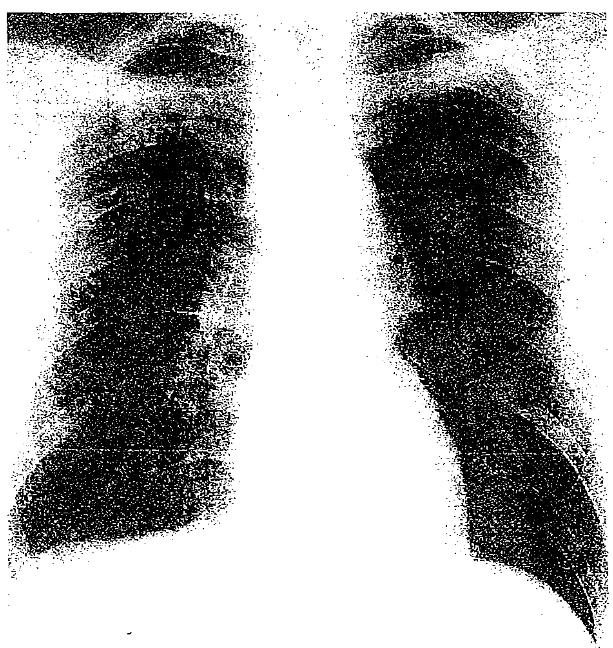


**Figure 60–9. Silicosis: Characteristic Radiographic Findings.** A posteroanterior chest radiograph demonstrates numerous well-defined small nodules mainly in the upper and middle lung zones. The nodules measure 1.5 to 3 mm in diameter (International Labour Office [ILO] q size nodules), and the profusion is 2/3 (slightly greater than the ILO standard radiograph for profusion 2/2 but considerably less than the standard for profusion 3/3). Early conglomeration is present near the lung apices.

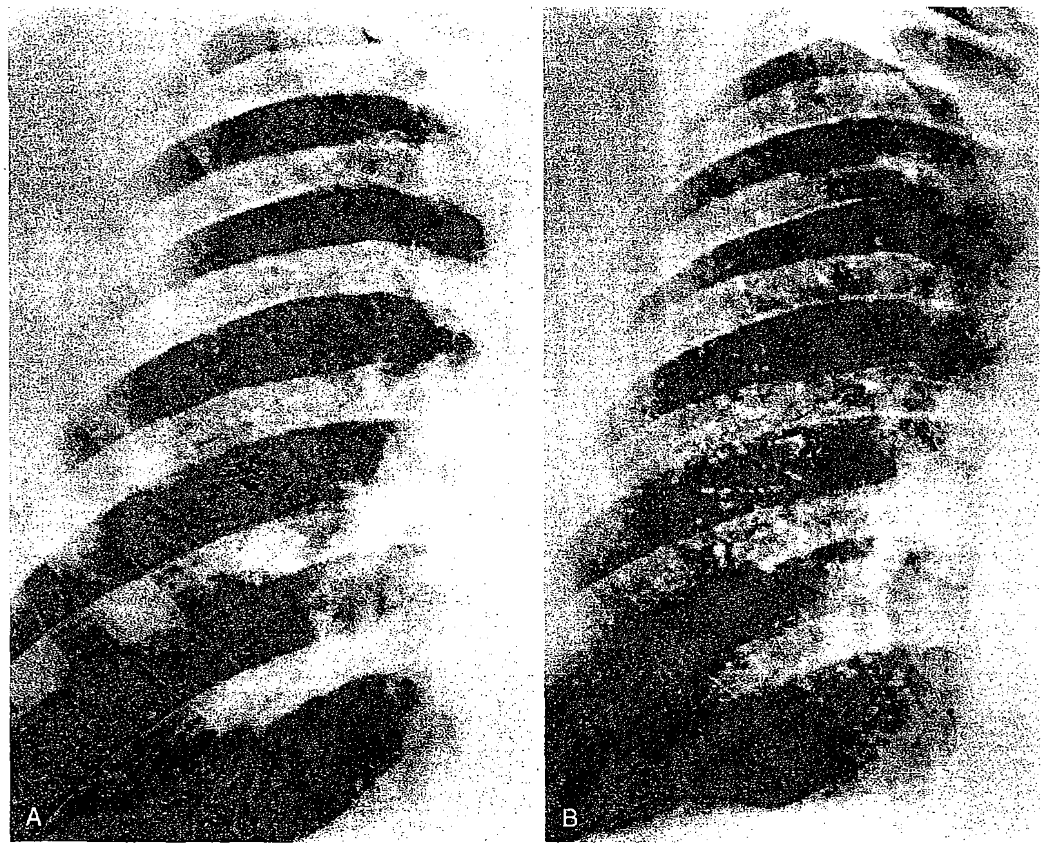



**Figure 60–10. Calcification of Silicotic Nodules.** A view of the right hemithorax from a posteroanterior radiograph of a 32-year-old man *(A)* reveals involvement of all lung zones by small irregular opacities of unit density. Eighteen years later *(B)*, multiple punctate calcifications had developed throughout the right lung, representing calcification of the silicotic nodules. The patient had a history of 26 years' work in South African gold mines. (Courtesy of Dr. Raymond Glynn-Thomas, Medical Bureau for Occupational Diseases, Johannesburg, South Africa.)

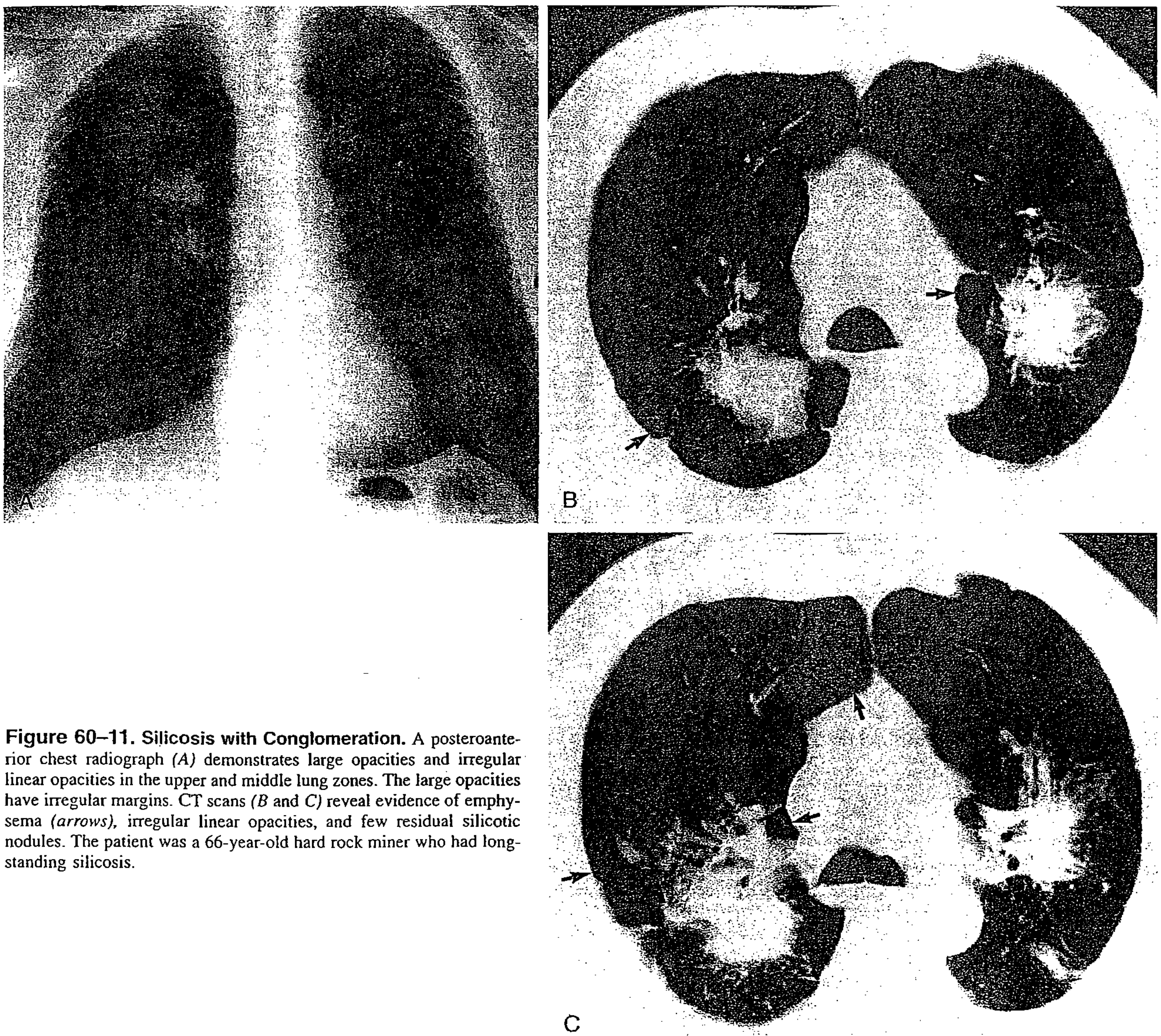



**Figure 60–11. Silicosis with Conglomeration.** A posteroanterior chest radiograph *(A)* demonstrates large opacities and irregular linear opacities in the upper and middle lung zones. The large opacities have irregular margins. CT scans *(B* and *C)* reveal evidence of emphysema *(arrows)*, irregular linear opacities, and few residual silicotic nodules. The patient was a 66-year-old hard rock miner who had longstanding silicosis.

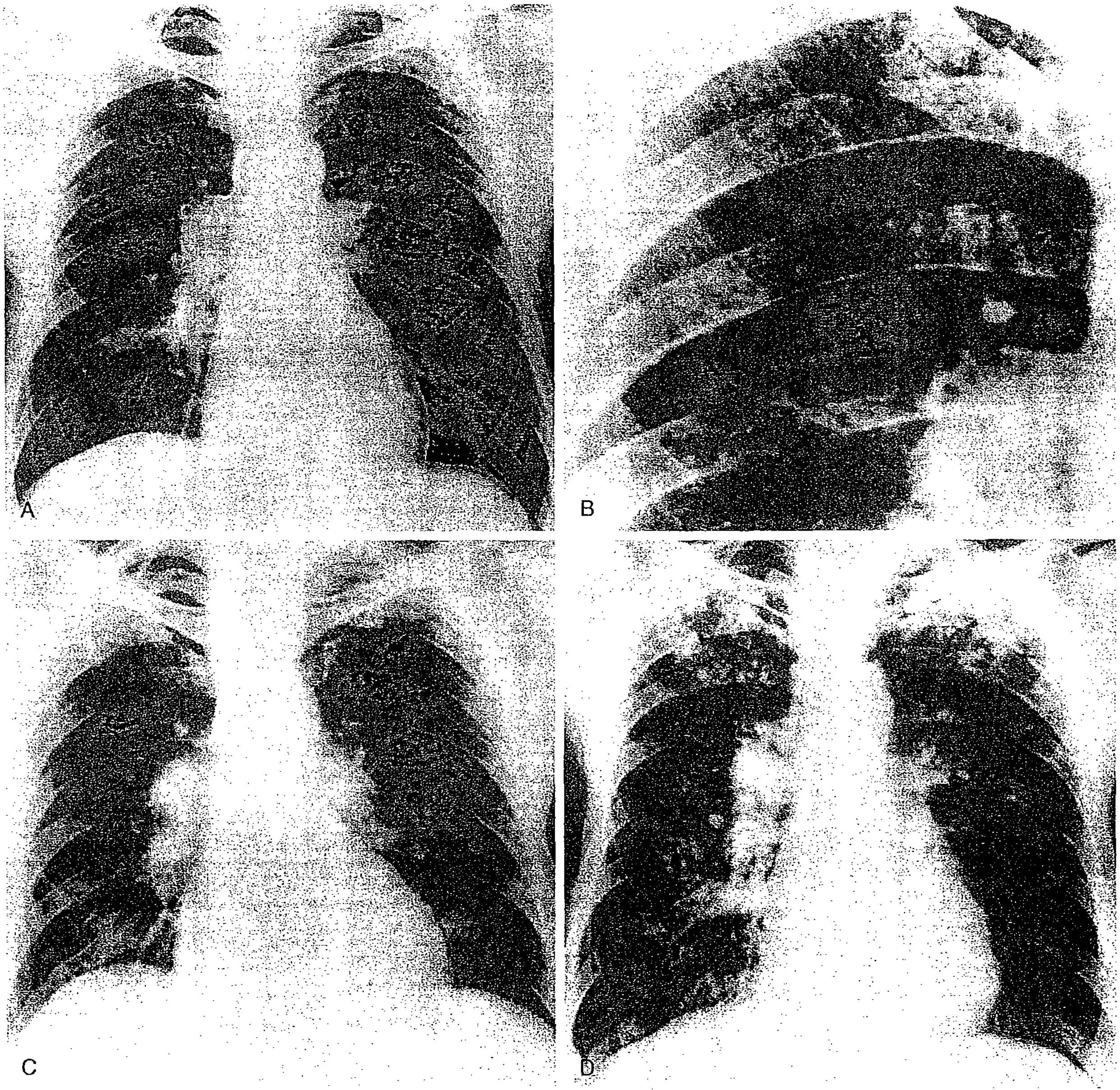



**Figure 60–12. Silicosis Progressing from Simple to Conglomerate.** A 54-year-old foundry worker was asymptomatic at the time of the first radiograph *(A)*. The opacities throughout both lungs are predominantly small and rounded and are more evident in the upper and mid zones than in the bases. The nodules are relatively discrete, as revealed in a magnified view of the right upper lung *(B)*. An exceptional degree of hilar lymph node enlargement is present bilaterally. Four years later *(C)*, the nodules are more numerous and have become confluent in the subapical zones bilaterally so as to form shadows of homogeneous density (conglomeration). A radiograph *(D)* taken 7 years after *C* reveals marked progression of the disease; not only are the nodules more numerous, but their density is considerably greater than had been observed earlier. By this time, confluence of shadows in the subapical zones had progressed considerably; one on the left had undergone cavitation *(arrow)*.

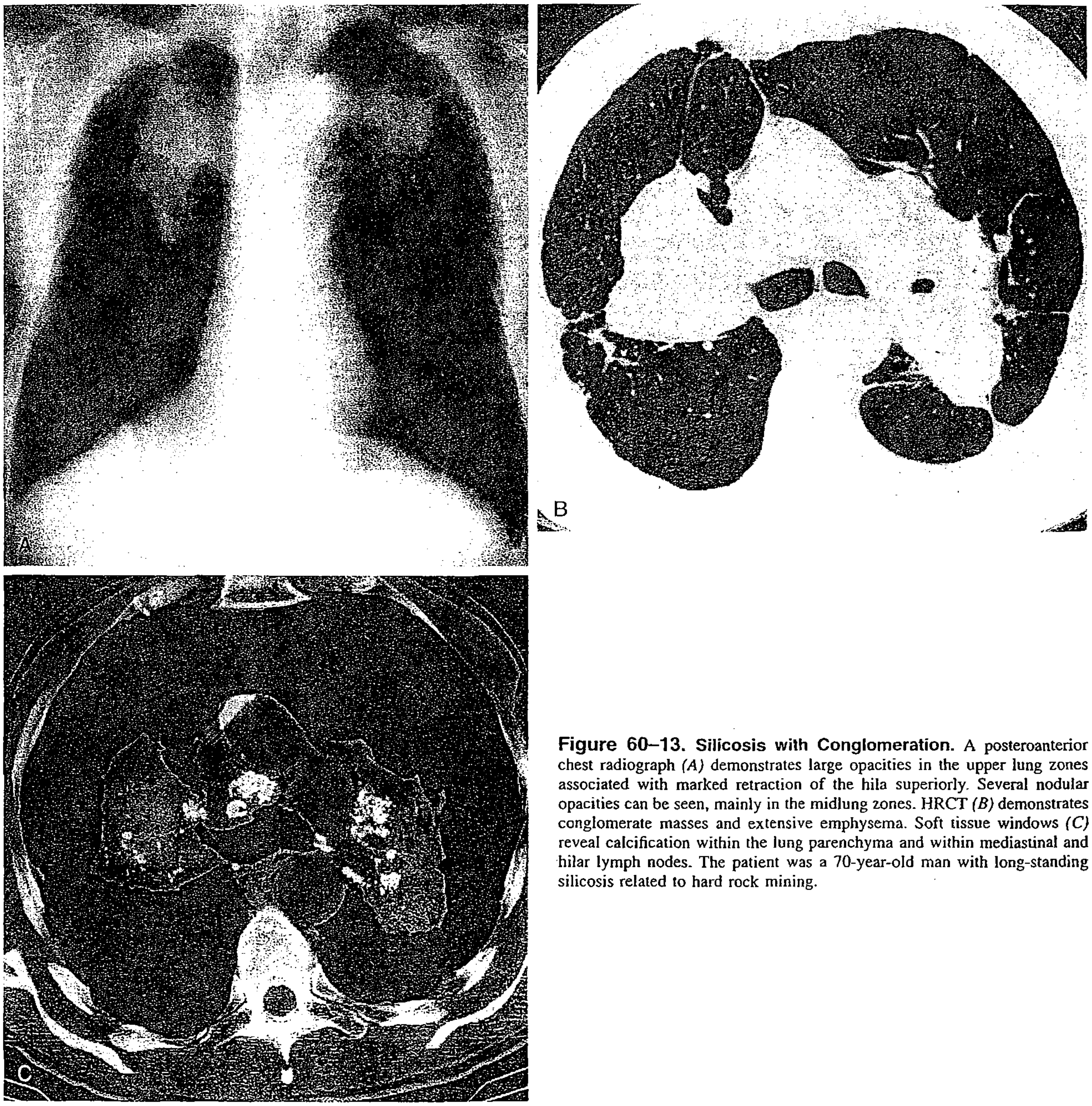
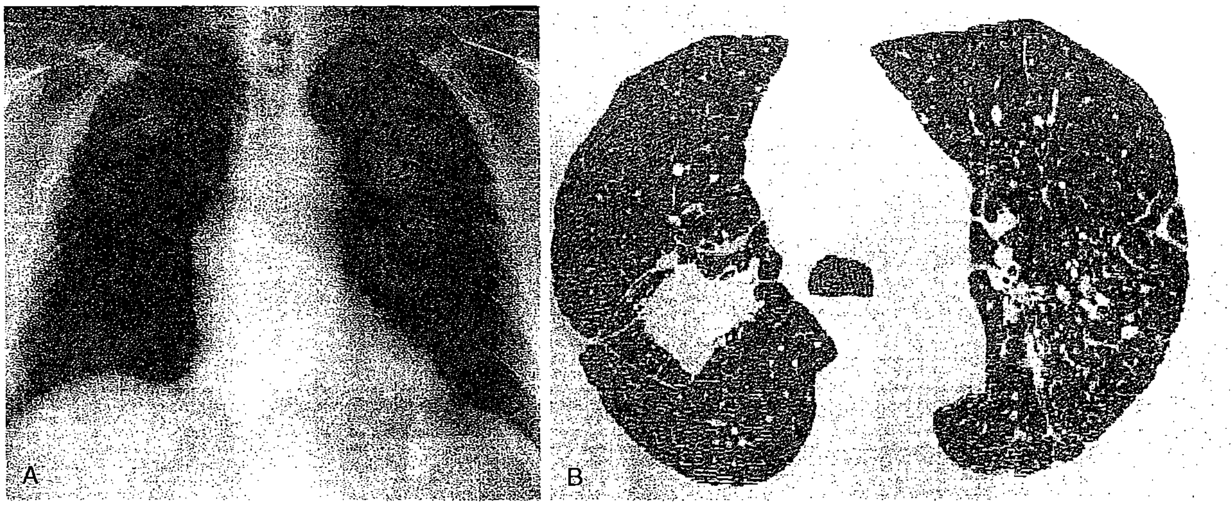



**Figure 60–13. Silicosis with Conglomeration.** A posteroanterior chest radiograph *(A)* demonstrates large opacities in the upper lung zones associated with marked retraction of the hila superiorly. Several nodular opacities can be seen, mainly in the midlung zones. HRCT *(B)* demonstrates conglomerate masses and extensive emphysema. Soft tissue windows *(C)* reveal calcification within the lung parenchyma and within mediastinal and hilar lymph nodes. The patient was a 70-year-old man with long-standing silicosis related to hard rock mining.



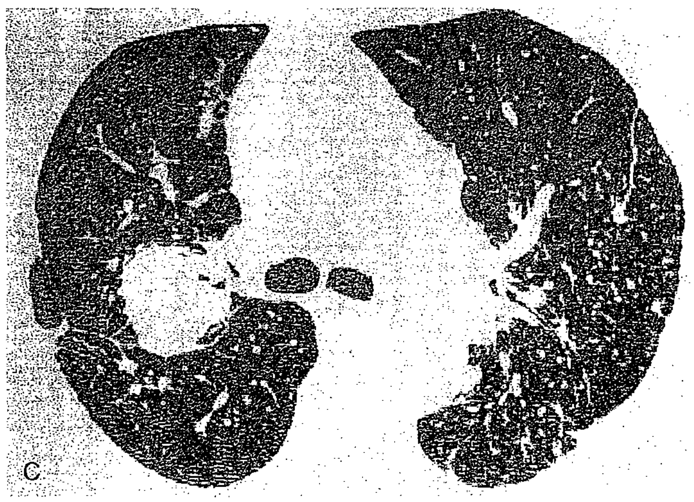




**Figure 60–14. Silicosis with Unilateral Conglomeration.** A posteroanterior chest radiograph *(A)* demonstrates a large opacity in the right upper and middle lung zones. Numerous small rounded opacities are present throughout the left lung; relatively few are seen in the right lung. HRCT scans *(B* and *C)* essentially confirm the radiographic findings. The conglomerate fibrosis has resulted in volume loss of the upper lobe. No evidence of conglomeration is present in the left lung on the radiograph or CT. The patient was a 68-year-old man with a history of mining and long-standing silicosis.

Hilar lymph node enlargement is common and may occur with or without associated silicosis (Fig. 60–15).[175, 176] Calcification is not uncommon—in one series of 1,905 cases, it was identified in 4.7%[177]—and characteristically tends to involve mainly the periphery of the nodes, a finding referred to as *eggshell calcification.* Although occasionally seen in other conditions (Fig. 60–16),[178, 178a] this pattern is almost pathognomonic of silicosis; its occurrence in coal and metal miners has been attributed to concomitant exposure to silica.[176] Although most common in the hilar lymph nodes, eggshell calcification also develops rarely in lymph nodes in the mediastinum[177] and the intra-abdominal and retroperitoneal areas.[178]

The enlarged lymph nodes may lead to problems in diagnosis in some patients. For example, enlarged silicotic nodes in the retroperitoneum have been confused with metastatic pancreatic carcinoma.[179] In one patient who had *Mycobacterium avium-intracellulare* infection, bronchial obstruction developed from broncholithiasis as a result of eroding infected silicotic nodes.[180] Mediastinal nodes may encroach on the phrenic nerve, resulting in unilateral diaphragmatic paralysis.[181] We have also seen one patient in whom enlarged hilar lymph nodes were associated with fibrosing mediastinitis resulting in obstruction of the right interlobar pulmonary artery (Fig. 60–17).

Ten to 20 years' exposure usually is necessary before the appearance of radiographic abnormalities.[182] The onset of disease is sometimes accelerated, however, particularly in patients exposed to high concentrations of dust in a relatively confined area.[183] Such disease has radiographic features similar to those of the classic form except that they develop over a period of only a few years (Fig. 60–18). As indicated previously, particularly large exposure to silica dust, such as may occur in sandblasters, can result in silicoproteinosis. This variant is characterized by bilateral parenchymal consolidation similar to alveolar proteinosis that progresses rapidly over a period of months or 1 or 2 years.[184, 185]

Another variant of classic silicosis is Caplan's syndrome, which consists of the presence of large necrobiotic nodules superimposed on a background of simple silicosis. It is a manifestation of rheumatoid lung disease and is seen more commonly in coal workers' pneumoconiosis than in silicosis (*see* page 2416). In a controlled study of patients who had silicosis with and without rheumatoid arthritis, the rate of progression of the silicosis was found to be greater in the former, as was the probability that the silicosis was

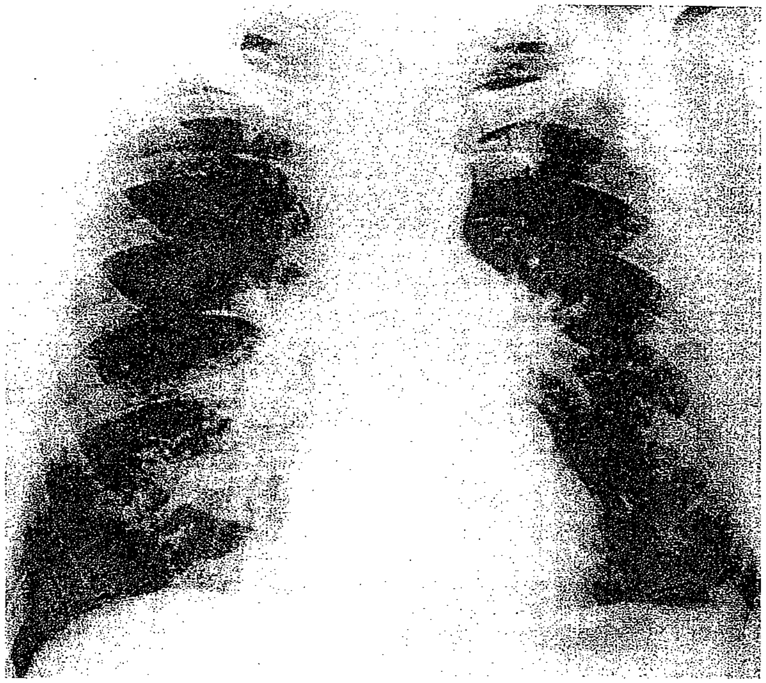


**Figure 60–15. Silicosis with Hilar Lymph Node Enlargement.** A posteroanterior radiograph reveals a rather coarse reticular pattern evenly distributed throughout both lungs. Hilar lymph nodes are enlarged bilaterally. This patient, a 57-year-old man, had worked underground in a gold mine for many years.

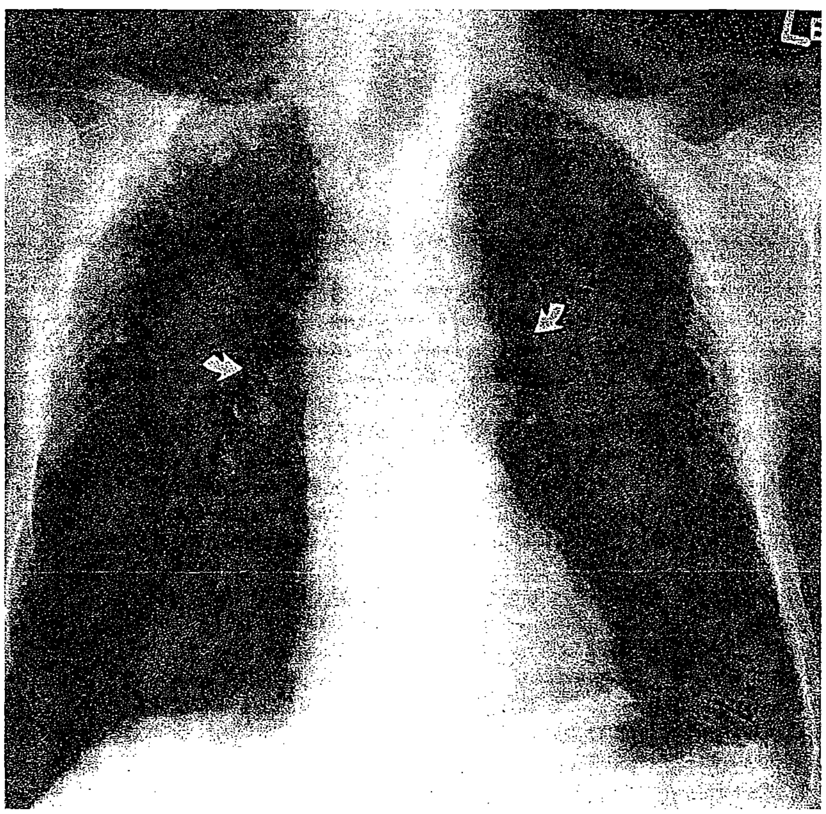


**Figure 60–16. Eggshell Calcification of Lymph Nodes in Silicosis.** A posteroanterior chest radiograph demonstrates numerous calcified silicotic nodules mainly in the upper lung and midlung zones. Several enlarged hilar and mediastinal lymph nodes are present with peripheral (eggshell) calcification *(arrows)*. The patient was a 78-year-old man who had been a miner for more than 20 years.

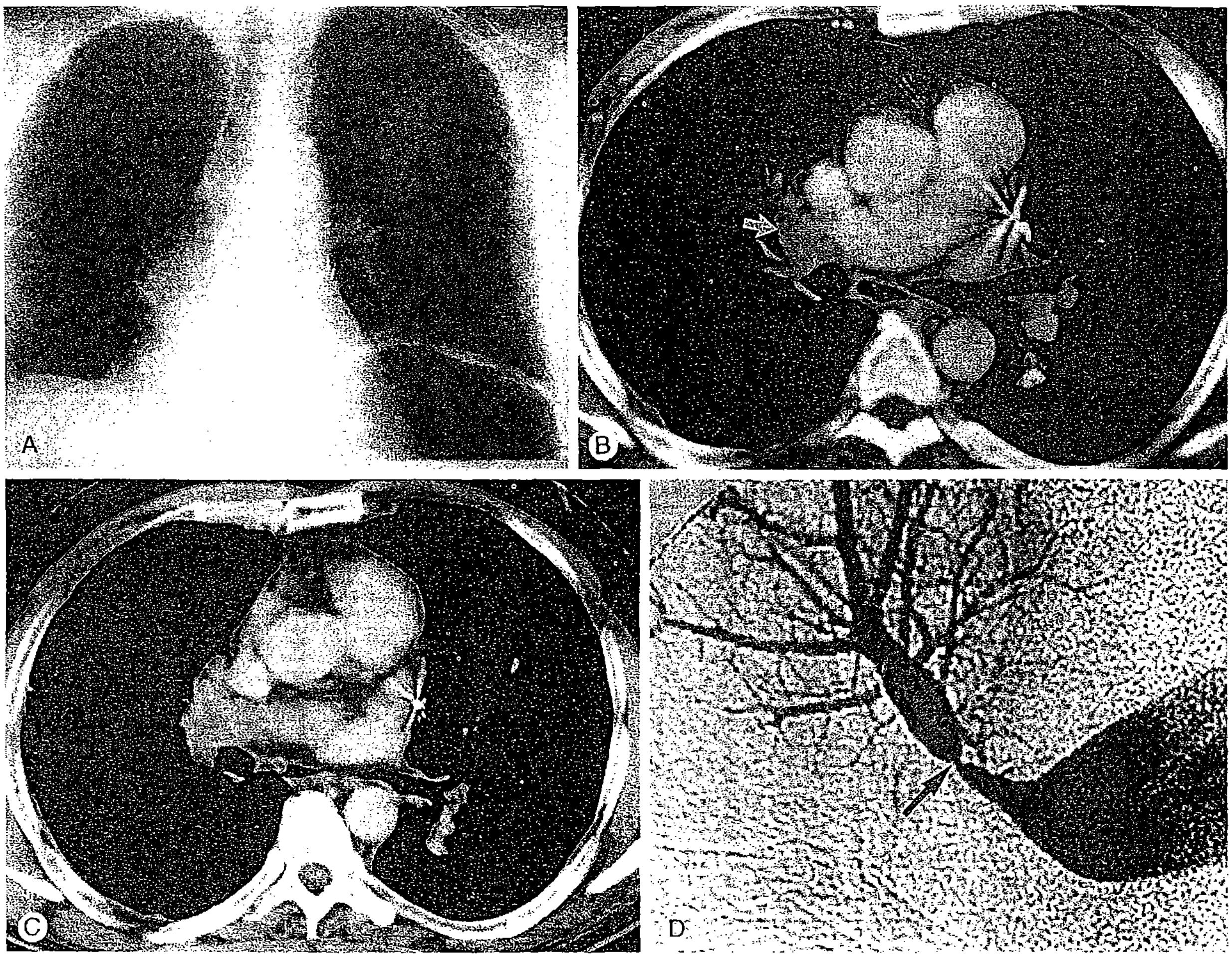



**Figure 60–17. Fibrosing Mediastinitis Due to Silicosis.** A 43-year-old man who had emigrated recently from India presented with progressive dyspnea. He had undergone previous left lower lobectomy for silicotuberculosis. He had no history of exposure to dust. A posteroanterior chest radiograph *(A)* demonstrates localized irregular linear opacities in both lungs and postoperative changes related to the previous lobectomy. The vascularity of the right lung is decreased. Contrast-enhanced CT scans *(B* and *C)* demonstrate nonenhancing soft tissue density in the region of the right interlobar pulmonary artery *(arrow)* causing obstruction to blood flow. A view from a selective right pulmonary angiogram *(D)* demonstrates complete obstruction of the right interlobar pulmonary artery and marked focal narrowing *(arrow)* of the artery to the right upper lobe. At surgery the patient was shown to have unresectable fibrosing mediastinitis. Pathologic assessment from surgical biopsy specimens demonstrated silicotic nodules in lymph nodes and surrounding tissue.

manifested by larger nodules (type r) at the time of presentation.[186]

Radiographic progression of silicosis after removal from exposure has been well established. For example, in one study of 1,902 workers who had no radiographic evidence of PMF a maximum of 4 years before leaving the occupation, 172 subsequently developed PMF on follow-up examination.[187] Despite the development of conglomerate lesions after leaving employment, this cohort of workers showed no overall progression or regression of the grades of simple pneumoconiosis.

The CT findings of silicosis have been described by several investigators.[172, 188–190] The characteristic abnormalities are similar to those on the radiograph: sharply defined small nodules that may be diffuse throughout the lungs but frequently are most numerous in the upper lung zones (Fig. 60–19). In patients who have relatively mild disease, the nodules may be seen only in the posterior aspect of the upper lobes.[172, 191] Nodules adjacent to the visceral pleura may appear as rounded or triangular areas of attenuation, which, when confluent, may simulate pleural plaques ("pseudoplaques") (Figs. 60–19 and 60–20). Confluent nodules (PMF) usually have irregular margins and may contain areas of calcification (*see* Fig. 60–13); surrounding emphysema is usually present. Hilar or mediastinal lymph node enlargement is also apparent in approximately 40% of patients.[191]

Distinction of small nodules from vessels is easier on conventional or spiral CT (*see* Fig. 60–19) than on HRCT (*see* Fig. 60–20).[192] The last-named technique, however, allows better assessment of fine parenchymal detail and of emphysema. Furthermore, HRCT may allow detection of nodules in patients who have normal radiographic and conventional CT findings[189] and is particularly helpful in the assessment of patients who have nodules less than 1.5 mm in diameter.[190] In one investigation of 49 patients exposed to silica dust in mines and foundries, 13 (40%) of 32 patients who had normal radiographs had evidence of silicosis on CT;[189] in three of these cases (10%), the abnormality was

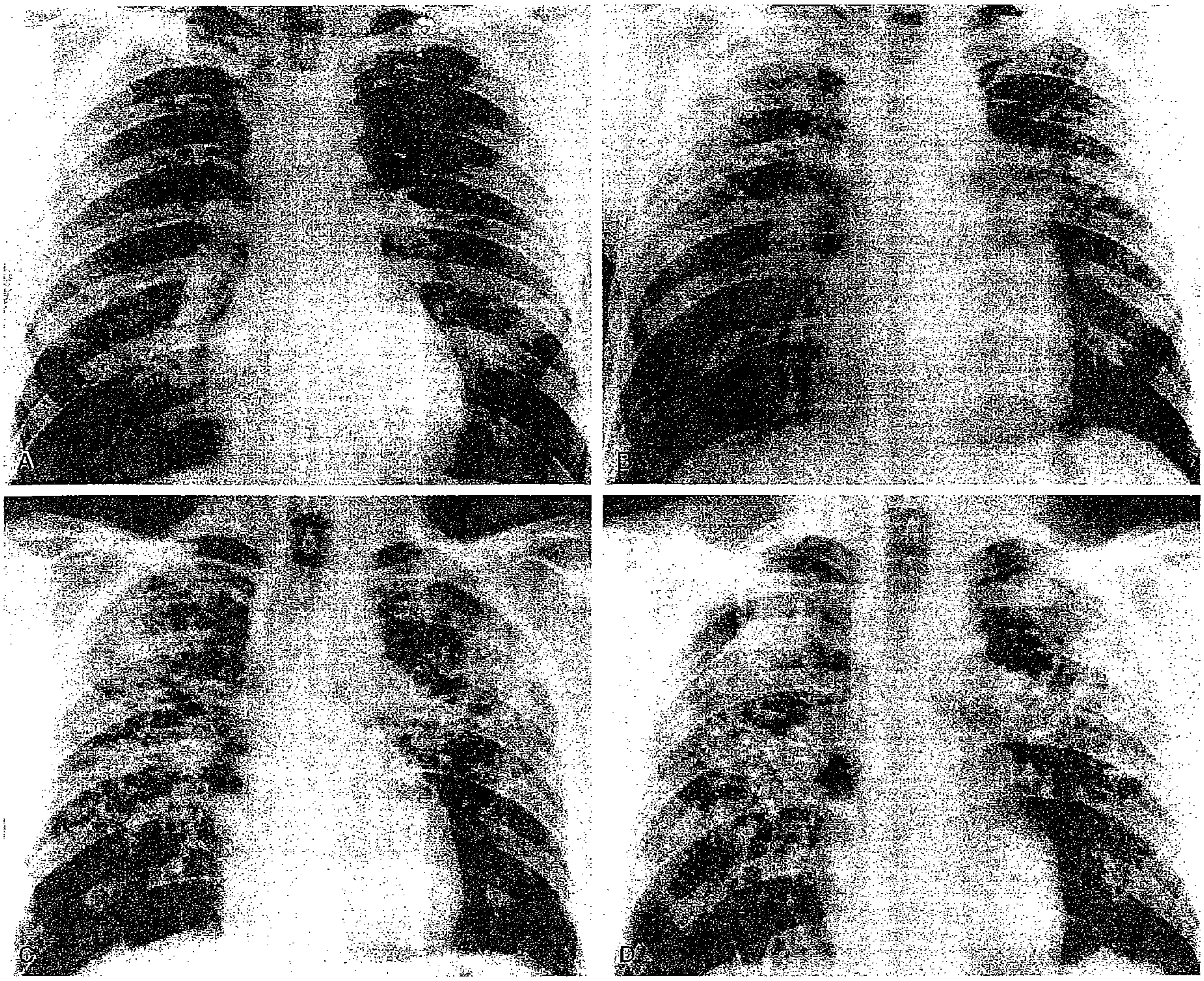


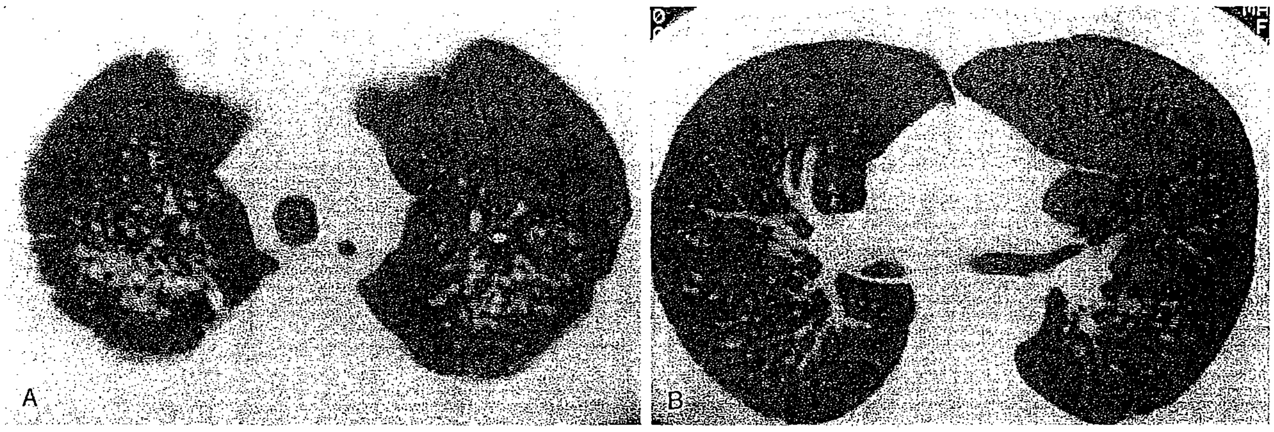

**Figure 60–18. Silicosis Showing Rapid Progression.** A radiograph of a 27-year-old sandblaster *(A)* reveals diffuse, predominantly irregular opacities more prominent in the upper lung zones; hilar lymph nodes are enlarged. Two years later *(B)*, lung volume had reduced somewhat, particularly in the upper lung zones (note the upward displacement of both hila). The opacities in the upper lungs were showing early coalescence. Three years later *(C)*, large opacities had developed in the upper lung zones, and 7 years after he was originally seen *(D)*, the large opacities had become much larger. Note the sharply defined lateral margin of the large opacity on the right.

visible only on HRCT. Conventional CT and HRCT may also allow detection of early confluence of nodules not apparent on the radiograph.[172, 189] Therefore in the assessment of patients who have possible silicosis, it is recommended that conventional or spiral CT scans be obtained and be supplemented by HRCT scans obtained at three to five levels through the upper lung and midlung zones.[192, 193]

The characteristic CT findings of PMF consist of focal soft tissue masses often with irregular margins and surrounded by areas of emphysema.[188, 189, 194] On magnetic resonance imaging (MRI), confluent nodules usually have signal intensity similar to that of muscle on T1-weighted images and lower signal intensity on T2-weighted images.[194a] Central areas of increased signal intensity on T2-weighted MR images may be seen; these have been shown to correspond to low attenuation on CT and are suggestive of necrosis.[194a]

In one study of 17 patients who had silicosis and 6 controls, the qualitative and quantitative assessment of silicosis on chest radiographs and CT scans was compared with the results of pulmonary function tests.[172] The extent of silicosis as assessed on CT was also compared with the extent estimated from chest radiographs using the ILO 1980 classification. Good correlation was found between the CT visual scores and the chest radiographic ILO profusion score ($r = 0.84$); however, there was poor correlation between the nodular profusion on the chest radiograph and CT with the functional impairment. A significant positive correlation was seen between the extent of emphysema on CT and the functional impairment as assessed by the $FEV_1$ per cent predicted ($r = 0.66$) and the diffusing capacity ($r = 0.71$). Emphysema associated with silicosis was easily detected on CT but not on the radiographs.

Emphysema in silicosis may be secondary to PMF or to other causes, particularly cigarette smoking. To distinguish these factors, one group of investigators compared the CT findings and pulmonary function tests in 18 patients who



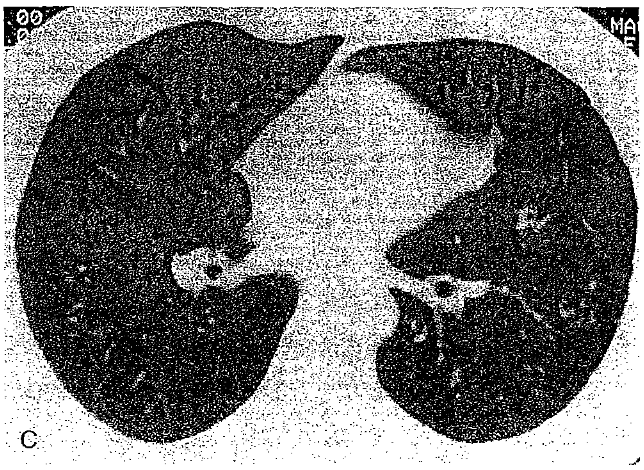




**Figure 60–19. Silicosis: Characteristic Findings on Conventional CT.** Conventional 10-mm collimation CT scans demonstrate numerous well-defined small nodules, most abundant in the posterior half of the upper lung zones *(A)*. CT at this level also demonstrates pseudoplaques (i.e., subpleural nodules resulting in an appearance resembling plaques). The nodules also have a perivascular distribution, most evident in the scan obtained through the midlung zones *(B)*. CT scan at the level of the inferior pulmonary veins *(C)* shows relatively few nodules. The patient was a 50-year-old miner.

had silicosis and who were ex-smokers or current smokers and 12 patients who had silicosis and were lifetime nonsmokers.[194] The extent of emphysema on CT correlated with airway obstruction as assessed by the $FEV_1$ and the decrease in carbon monoxide diffusing capacity (DLCO), independent of its association with either cigarette smoking or grade of silicosis. The severity of silicosis was associated with a decrease in DLCO independent of its association with either cigarette smoking or per cent emphysema but did not correlate with the $FEV_1$. Among the patients who did not have PMF, smokers had worse emphysema than nonsmokers; however, there was no such difference among patients who had PMF. One of the nonsmoking subjects who had silicosis but did not have PMF had evidence of emphysema on CT.

### Clinical Manifestations

The diagnosis of silicosis usually is based on the identification of a diffuse nodular or reticulonodular pattern on the chest radiograph of a patient who has an occupational history compatible with exposure to dust containing high concentrations of $SiO_2$. In contrast to many other inhalation diseases caused by inorganic and organic dusts, the fibrosis and associated disability in silicosis frequently are progressive, even after removal of the patient from the dusty environment.[195] Thus, it is not uncommon for a patient to present with symptoms many years after leaving the occupation responsible for the dust exposure. This is an important point to remember because only a complete occupational history, ranging over a patient's entire working life, may provide the clue to the diagnosis.

Many patients are asymptomatic when first seen. Some complain of shortness of breath, initially on exertion only but becoming increasingly severe as the radiographic abnormalities worsen. As might be expected, dyspnea has been found to be more common in patients who have radiographic evidence of silicosis than in individuals who have silica exposure and normal chest radiographs.[196] In one series of hospitalized patients who had silicosis, crackles and wheezes were evident in the majority;[197] however, in our experience, asymptomatic ambulatory patients who have silicosis usually have no adventitious sounds on auscultation. With progressive destruction of pulmonary tissue, pulmonary hypertension, cor pulmonale, and, eventually, right-sided heart failure develop. The major pulmonary abnormality associated with the development of cor pulmonale appears to be the severity of associated emphysema, the extent of fibrosis being of lesser importance.[198]

In contrast to classic silicosis, in which the great majority of patients are asymptomatic and an exposure of 10 to 20 years is required before the disease becomes evident radiographically, a small number of patients develop symptomatic disease within 5 to 10 years of exposure (so-called

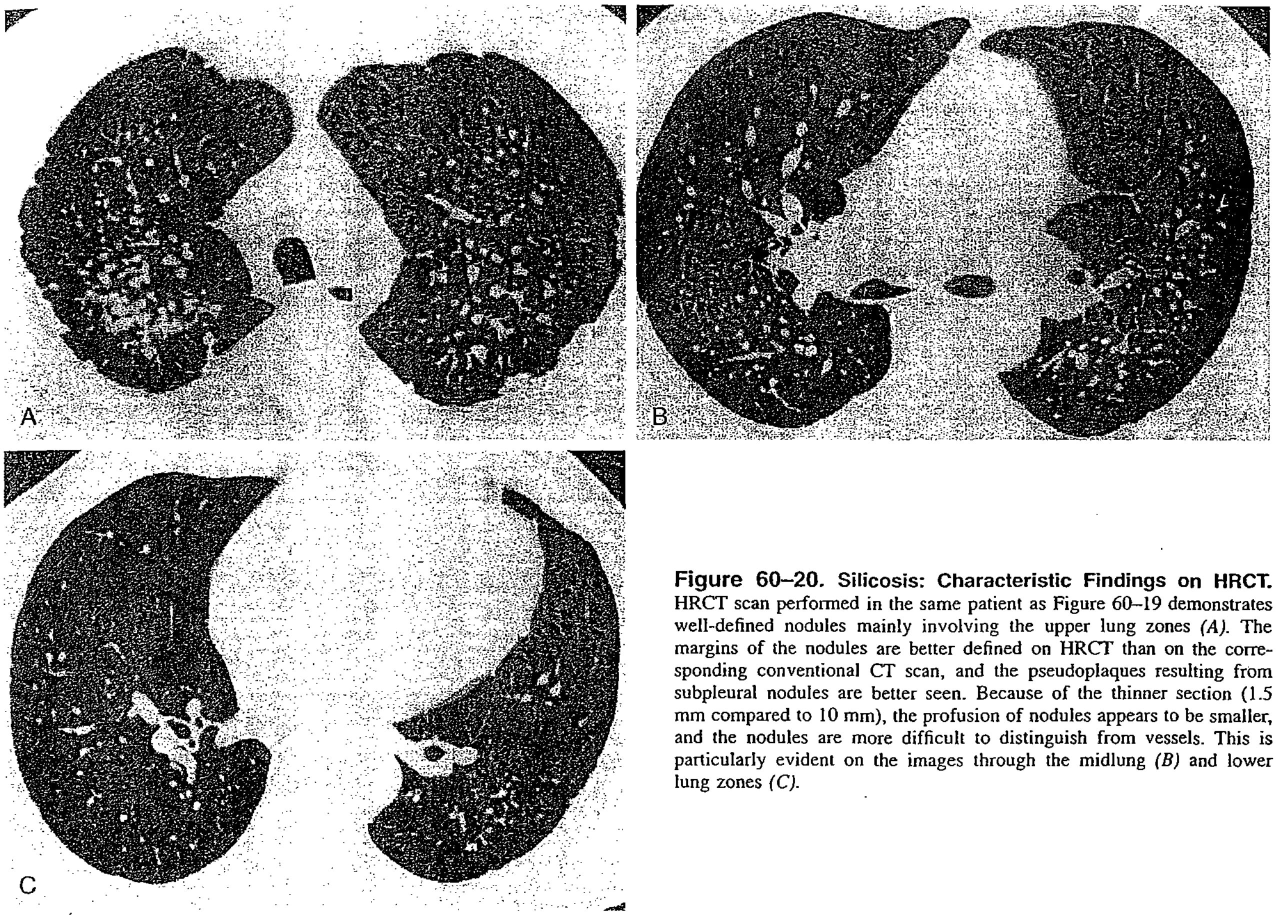



**Figure 60–20. Silicosis: Characteristic Findings on HRCT.** HRCT scan performed in the same patient as Figure 60–19 demonstrates well-defined nodules mainly involving the upper lung zones *(A)*. The margins of the nodules are better defined on HRCT than on the corresponding conventional CT scan, and the pseudoplaques resulting from subpleural nodules are better seen. Because of the thinner section (1.5 mm compared to 10 mm), the profusion of nodules appears to be smaller, and the nodules are more difficult to distinguish from vessels. This is particularly evident on the images through the midlung *(B)* and lower lung zones *(C)*.

accelerated silicosis). Apart from its relatively early onset and rapid progression, the radiographic, clinical, and pathologic features of this variant are identical to those of more classic disease. Although this form is probably less common today than previously as a result of dust control in the workplace, cases are still observed in conditions of environmental neglect.[85]

Silicoproteinosis is another relatively acute and even more rapidly progressive form of disease. This variant was reported initially in quartzite millers[199] and workers in the scouring powder industry;[71, 72] it has also been described in tunnel workers, silica flour workers,[199] and sandblasters.[155, 200, 201] The last-named often remove their masks after sandblasting and then proceed to paint in the dusty atmosphere; when disease develops, it often leads to death as a result of respiratory failure, not uncommonly with a complicating pneumothorax.[200]

The combination of an occupational history and typical radiographic changes usually suffices to permit confident diagnosis of silicosis. Occasionally, it is necessary to confirm the diagnosis with tissue samples. In some instances, histologic features of biopsy specimens are sufficient for diagnosis. Although transbronchial or open biopsy specimens are probably the most efficacious in this regard, the diagnosis has also been made by needle biopsy; in one study, the core of tissue was considered to be compatible with silicosis in almost two thirds of patients in whom the final diagnosis was confirmed.[202] In other cases, chemical analysis of lung ash content, scanning electron microscopy, and x-ray energy spectrometry of tissue specimens have been used.[203, 204] X-ray microanalysis has also been used to examine BAL fluid obtained from patients who have a history of exposure to silica, either with or without silicosis;[205] somewhat surprisingly, quantification was unable to distinguish between exposed and affected workers. The false-negative rate was almost 15% and the false-positive rate 5%, using unexposed individuals who did or did not have intestinal lung disease as controls.

Bronchoscopy may show evidence of airway stenosis, sometimes resembling carcinoma.[167a] The mucosa may have a gray or even black appearance as a result of the extension of arthracotic-pigment containing macrophages from adjacent lymph nodes (however, a similar appearance can be seen in association with tuberculous bronchostenosis).

### Laboratory Findings

Silicosis is accompanied by a rise in angiotensin-converting enzyme;[206–209] in fact, high serum levels of the enzyme have been found to correlate with progression of the disease.[208] As mentioned previously, serologic abnormalities, including the presence of rheumatoid factor, antinuclear antibodies,[128] and immune complexes,[129, 130] are common. A

polyclonal increase in gammaglobulin is also seen in some patients.[130, 131]

### Pulmonary Function Tests

Quantification of clinical disability is often necessary for compensation purposes; pulmonary function tests are essential in this regard. (When interpreting these tests, it is important to remember that the effects of silicosis and dust exposure on lung function may be confounded by those of cigarette smoking.) Function may be normal in the early stages of disease,[210, 211] and exercise testing is not more sensitive than routine lung function in demonstrating early impairment.[212] Higher degrees of profusion of simple nodular silicosis may be associated with significant loss of lung function,[213] however, as well as a greater loss of function over time than is seen in workers who have lesser degrees of profusion, after correction for smoking history, age, and initial lung function values.[214] When dyspnea is present, impairment of function may be obstructive, restrictive, or a combination of both.[213, 215, 216] Diffusing capacity may be decreased;[210, 215, 217] the combination of this finding with hyperinflation and decrease in flow rates constitutes a pattern of functional impairment identical to that of uncomplicated pulmonary emphysema. Although arterial oxygen saturation may be normal at rest, exercise gives rise to hypoxemia, particularly in patients who have PMF.[215, 218] In the late stages of the disease, carbon dioxide retention may develop.[219] Conglomeration of nodules is associated with a significant reduction in lung compliance, lung volumes, and diffusing capacity.[220]

The observation that significant emphysema in nonsmoking silica-exposed workers is relatively rare[203, 210, 211, 215] has been used by many clinicians to argue against a relationship between dust exposure and the development of chronic air-flow obstruction. This argument, however, does not allow for the potential synergistic effects of dust and tobacco smoke;[221] moreover, it ignores the results of studies that demonstrate functionally important airway damage in both experimental animals[222] and nonsmoking workers who have been exposed heavily to dust (*see* page 2174).[223–226] Several examples suffice to illustrate this relationship. The risk of developing significant emphysema has been shown in one investigation to be 3.5 times greater in miners heavily exposed to dust compared with miners who have lighter dust exposures.[227] In one autopsy study of 242 nonsmoking South African gold miners who had undergone pulmonary function testing within a few years of death, advanced silicosis was associated with a significant degree of both air-flow obstruction and restriction.[228] Investigations of Vermont granite workers in which there was appropriate control for the effects of age and smoking have revealed excessive loss of $FEV_1$ with time in the dust-exposed individuals in the absence of radiologic evidence of silicosis[226] as well as more rapid development of small airway abnormalities with increasing dust exposure in both smokers and nonsmokers.[229] These results have been confirmed in a French study of silica-exposed workers;[230] similar effects on the $FEV_1$ have been documented in granite quarry workers from Singapore[231] and retired miners from Colorado.[232] In another study in which emphysema grade was determined by HRCT, a significant excess of emphysema and pulmonary function abnormalities was found in workers who had silicosis and in dust-exposed workers who did not have the disease, after controlling for age and smoking history.[233] The evidence supports the hypothesis that the dusty environment of silica-exposed workers can contribute to the development of chronic air-flow obstruction and emphysema.

### Prognosis and Natural History

Symptomatic patients who have silicosis have a poorer prognosis than asymptomatic patients; in fact, asymptomatic patients who have simple nodular silicosis have a life expectancy similar to that of the general population.[234] In patients with silicosis, older age is associated with increased mortality.[234, 235] The prognosis and natural history of silicosis are also related to two serious potential complications—carcinoma and tuberculosis.

#### *Relationship to Neoplasia*

In 1996, silica was recognized as an occupational carcinogen by the International Agency for Research on Cancer.[236] The strength of the association is much greater for workers who have silicosis[237–243, 274, 274a] than for those who have been exposed to silica but have no evidence of the disease.[227, 244–247] The relative risk for pulmonary carcinoma among the former patients often exceeds 3.0 and has been found to be as high as 6.0 in some studies;[241, 248] by contrast, the relative risk of carcinoma in the absence of silicosis has been estimated to be 1.3.[249] The excess risk has been reported in workers in industries unassociated with exposure to other occupational carcinogens, such as stone cutters,[250–252] and has been shown to be independent of cigarette smoking.[227, 241, 242, 246, 248, 253–255] These relationships are discussed in detail in Chapter 31 (*see* page 1077).

#### *Relationship to Pulmonary Tuberculosis*

There is little question that silicosis predisposes to tuberculosis;[256] however, the prevalence of this complication in workers who have silicosis depends to a large extent on the prevalence of tuberculosis in the population from which the workers come.[257] Although it is customary to associate the development of tuberculosis with the presence of PMF, there is evidence that its risk increases with increasing profusion of simple nodular shadows;[258] the likelihood of developing tuberculosis is greater in workers who have any degree of silicosis compared with similarly exposed workers without silicosis.[258] In patients who have silicosis, the development of tuberculosis is a strong independent predictor of mortality.[235] It may be extremely difficult to isolate tubercle bacilli during life in patients who have tuberculosis and silicosis, particularly those who have PMF, despite postmortem demonstration of active tuberculous infection;[259] identification of organisms by polymerase chain reaction might prove to be useful in this setting.[260]

#### *Relationship to Connective Tissue Disease*

The association of progressive systemic sclerosis with silicosis and with exposure to high concentrations of silica

dust is well established.[90] The evidence for a similar association of silicosis and rheumatoid arthritis is less clear; however, if real, it is unlikely to be strong.[90] A causal association between systemic lupus erythematosus and silica exposure should be suspected only in the presence of acute or accelerated silicosis.[90]

## COAL AND CARBON

The inhalation and retention in the lung of dust composed predominantly of carbon (often termed *anthracosis*) is seen in many individuals,[261] particularly those who smoke or live in a city or industrial environment. Microscopically, such material is easily recognized as dense black particles, mostly 1 to 2 μm in size, within macrophages adjacent to terminal or proximal respiratory bronchioles and in the pleura. The material is also commonly present in bronchopulmonary, hilar, and mediastinal lymph nodes to which it characteristically imparts a distinct blackness on gross examination. Although predominantly composed of carbon, the particles also contain traces of other substances, such as silica and iron. Nevertheless, associated fibrosis or emphysema is invariably minimal or absent (except when associated with cigarette smoking), and it is generally believed that the presence of such particles is of no pathologic or functional significance.

Such innocuous environmental anthracosis is caused by the inhalation of relatively small amounts of dust. Inhalation of large amounts of carbonaceous material, however, either in the form of coal dust or as substances derived from coal or petroleum products, can be associated with significant pulmonary disease. Because quantity is important in this effect, such disease occurs almost exclusively in the workplace, where the concentration of these materials is much greater than that in nonoccupational settings. The most important occupation in terms of the number of individuals affected is coal mining, the resulting disease being appropriately called *coal workers' pneumoconiosis*. Workers involved in the production or use of graphite,[262–266] carbon black,[267] and carbon electrodes[268] are affected less often. The possibility that pulmonary disease is occasionally caused by inhalation of fly ash has also been suggested.[269, 270]

### Epidemiology

#### *Coal*

Coal is a sedimentary rock formed by the action of pressure, temperature, and chemical reactions on vegetable material. The percentage of pure carbon varies with different types, brown coal and lignite containing the least and anthracite the most.[271] The degree of exposure to carbon dust thus depends to some extent on the type of coal being mined, a feature that may partly explain the variability in incidence of CWP from colliery to colliery. Perhaps more important in this regard are local geologic variations;[272] some coal seams are thick (up to 100 feet), whereas others are much thinner and are separated by seams of silica-containing rock.[271] Mining in the latter situation can result in significant concomitant exposure to silica and other substances, a feature that probably explains the occurrence of classic silicosis in a small percentage of coal miners.[272, 273, 275]

Certain occupations within the coal mine are also associated with different likelihoods of developing disease and the form that such disease takes. For example, because the majority of dust is produced at the coal face,[275] workers of cutting and loading machines are at greater risk than those involved in transportation or maintenance at the mine surface. Similarly, miners drilling through quartz and workers involved in the maintenance or construction of underground roadways or the transportation of coal to the surface by railway (during which time sand has been put on the rails to increase traction) are more likely to come in contact with silica and to develop classic silicosis.[271, 273]

The impact of U.S. federal legislation in 1969, in which substantially lower dust levels were mandated for American coal mines, is now being felt, and the prevalence of CWP in the United States is less than it used to be.[276] Because current allowable dust levels of 2 mg/M$^3$ are sufficient to result in pneumoconiosis and because workers who have had previous, more intense dust exposures may still be in the workforce, new cases of the disease will undoubtedly continue to be identified.

With current environmental standards, it is estimated that 2% to 12% of American coal miners will develop category 2 or greater disease after a 40-year working life, whereas approximately 1% to 7% will develop PMF.[277, 278] These estimates are slightly in excess of those calculated for British underground miners, in whom simple pneumoconiosis has been predicted to develop in 9% and PMF in 0.7%.[279] Although these figures are comparable to those 30 years ago, they would represent a distinct improvement in disease prevalence compared to earlier in the century: surveys carried out in the early 1970s in the Appalachian region of the United States showed that approximately 10% of active coal miners had pneumoconiosis, about a third of whom had PMF;[280, 281] by contrast, an earlier review of a similar population showed that almost 50% of miners had simple pneumoconiosis, and 15% had complicated disease.[282] Most of these latter workers likely retired from the workforce as a result of their disease with resulting improvement in prevalence statistics in the later studies.[283]

#### *Other Carbonaceous Substances*

*Fly ash* is the solid residue that remains after the combustion of coal; the particles so formed are composed of a variety of elements, including silica, aluminum, and iron.[269] Because of these substances, workers in occupations associated with a high concentration of fly ash are theoretically at risk for developing pneumoconiosis; in fact, a high content of such particles has been demonstrated in the lungs of some individuals who have pulmonary fibrosis.[269, 270] Nevertheless, the majority of clinical and experimental evidence suggests that this material is not fibrogenic.[284]

*Graphite* (crystalline carbon) occurs both naturally as a mineral and as an artificial substance derived from heated coal or coke. It is used in the manufacture of steel, lubricants, lead pencils, nuclear reactors, and electrodes.[285] Pulmonary disease identical to CWP has been described occasionally in individuals engaged in these occupations.[262–266]

*Carbon black* is produced from the flames of natural